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Anees Ahmad

Explorando a Contração de Anel Mediada por
Iodo(III): Novos Substratos, Novas Condições e
Reações Assimétricas

Exploring the Iodine(III)-Mediated Ring Contraction: New Substrates,
Novel Conditions and Asymmetric Reactions

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Contraction: New Substrates, Novel Conditions
and Asymmetric Reactions**

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“Explorando a contração de anel mediada por iodo(III): novos substratos, novas condições e reações assimétricas”

ANEES AHMAD

Tese de Doutorado submetida ao Instituto de Química da Universidade de São Paulo como parte dos requisitos necessários à obtenção do grau de Doutor em Ciências - Área: Química.

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28 de agosto de 2015

*Dedicated to my late father and mother
who unfortunately didn't stay in
this world long enough to see
his son become a graduate.*

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Abstract

Ahmad, A. “**Exploring the Iodine(III)-Mediated Ring Contraction: New Substrates, Novel Conditions and Asymmetric Reactions**” 2015. (p.430). Ph.D. Thesis - Graduate Program in Chemistry. Institute of Chemistry, University of São Paulo, São Paulo Brazil.

In the first section this thesis includes the reactivity of various oxygen-containing benzofused cyclic alkenes with HTIB (Hydroxy(tosyloxy)iodobenzene). Instead of getting ring contraction products, *2H*-chromene resulted in *4H*-chromenes together with *trans*-addition products. Only *cis*-addition products were isolated from 4-methyl-*2H*-chromene. Ring contraction was observed in dihydrobenzoxepines and 2,2-dimethyl-*2H*-chromenes giving functionalized chromanes and benzofurans, respectively.

In the second part, the ring contraction of 1,2-dihydronaphthalenes using HTIB was expanded to substrates bearing oxygen and nitrogen substituents in the aromatic ring. The *N*-protecting groups Fmoc and Bz are stable under the reaction conditions giving indanes in 64-77% yield. The Ts-protected substrate gave only addition products. Acetoxy and benzoyloxy alkenes afforded indanes in 60-71% yield.

A new and efficient method for the oxidative rearrangement (ring contraction and expansion) of alkenes using *in situ* generated iodine(III) is described in the third section. The protocol uses inexpensive and stable chemicals (PhI, *m*CPBA and TsOH) furnishing rearrangement products in yields comparable to those obtained using commercially available iodine(III). Additionally, a new route for the one step transformation of 4-methyl-1,2-dihydronaphthalene into 1-methyl-2-tetralone using *m*CPBA and TsOH was developed.

In the last section is presented the reactivity of chiral iodine(III) with 1,2-dihydronaphthalenes. The hypervalent iodine species is generated *in situ* from chiral aryl iodide, which is prepared in one high yield step from inexpensive starting materials. Protected (Ac, Bz and Fmoc) amine alkenes gave indanes in 60-75% and 58-64% *ee*. In the same way, oxygenated substrates afforded acetal in 41-61% yield and 54-78% *ee*. Ring contraction products were

obtained in 77-88% yield and 34-40% *ee* when 1-methyl and aryl substituted alkenes were utilized.

Key words: ring contraction, chromanes, benzofurans, oxidative rearrangement, indane, chiral iodine(III), hypervalent iodine

Resumo

Ahmad, A. " **Explorando a Contração de Anel Mediada por Iodo(III): Novos Substratos, Novas Condições e Reações Assimétricas**" de 2015. (p.430). Ph.D. Tese - Programa de Pós-Graduação em Química. Instituto de Química, Universidade de São Paulo, São Paulo Brasil.

A primeira parte desta tese inclui a reatividade de vários alquenos benzofundidos cíclicos contendo oxigênio com HTIB (Hidróxi(tosilóxi)iodobenzeno). Em vez de obter os produtos de contração de anel, *2H*-cromeno resultou em *4H*-cromenos, juntamente com produtos *trans*-adição. Apenas produtos de adição de *cis* foram isolados a partir de 4-metil-*2H*-cromeno. Contração do anel foi observada em di-hidrobenzoxepinas e 2,2-dimetil-*2H*-cromenos dando cromanos funcionalizados e benzofuranos, respectivamente.

Na segunda parte, a contração de anel de 1,2-di-hidronaftalenos usando HTIB foi expandida para substratos contendo substituintes de oxigênio e de nitrogênio no anel aromático. Os grupos *N*-protetores Fmoc e Bz são estáveis sob as condições de reação fornecendo indanos em 64-77% de rendimento. O substrato protegido com Ts deu apenas os produtos de adição. Acetóxi e benzoilóxi alquenos geraram indanos em 60-71% de rendimento.

Um método novo e eficiente para o rearranjo oxidativo (contração e expansão do anel) de alquenos utilizando iodo(III) gerado *in situ* é descrito na terceira parte. O protocolo utiliza reagentes baratos e estáveis (PhI, *m*CPBA e TsOH) fornecendo produtos de rearranjo com rendimentos comparáveis aos obtidos utilizando iodo(III) disponível comercialmente. Além disso, um método para a transformação em uma etapa de 4-metil-1,2-di-hidronaftaleno em 1-metil-2-tetralona utilizando *m*CPBA e TsOH foi desenvolvido.

Na última parte é apresentada a reatividade de iodo(III) quiral com 1,2-di-hidronaftalenos. A espécie de iodo hipervalente é gerada *in situ* a partir de iodeto de arila quiral, o qual é preparado em uma etapa em rendimento elevado a partir de materiais de partida baratos. Amino alquenos protegidos (Ac, Bz e Fmoc) deram indanos em 60-75% de rendimento e 58-64% *ee*. Da mesma forma, os substratos oxigenados proporcionaram acetais em 41-61% de

rendimento e 54-78% de *ee*. Produtos de contração de anel foram obtidos em 77-88% de rendimento e 34-40% de *ee* quando alquenos 1-metil e aril substituídos foram utilizados.

Palavras-chave: contração de anel, cromanos, benzofuranos, rearranjo oxidativo, indano, iodo(III) quirál, iodo hipervalente.

Abbreviation List

α	Alpha
ACN	acetonitrile
Ac ₂ O	Acetic anhydride
Ar	Aryl
atm.	Atmosphere
β	Beta
Bz	Benzoyl
Cat.	Catalytic
¹³ C NMR	Carbon-13 nuclear magnetic resonance
Conc.	Concentrated
CSA	Camphorsulfonic acid
d	Doublet
dba	Dibenzylideneacetone
DCC	N,N'-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DIB	Diacetoxiyodo benzene
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
d.r.	Diastereomeric excess
<i>ee</i>	Enantiomeric ratio
Equiv	equivalent
Fmoc	Fluorenylmethyloxycarbonyl
GC	Gas chromatography
HFIP	1,1,1,3,3,3-hexafluoroisopropanol

^1H NMR	Hydrogen nuclear magnetic resonance
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HTIB	Hydroxy(tosyloxy)iodobenzene
IR	Infrared
IUPAC	International Union of Pure and Applied Chemistry
LRMS	Low resolution mass spectrometry
m	Multiplet
<i>m</i>	<i>meta</i>
<i>m</i> CPBA	<i>meta</i> -Chloroperbenzoic acid
Mes	Mesityl
Ms	methanesulfonyl
NOESY	Nuclear Overhauser effect spectroscopy
<i>o</i>	<i>Ortho</i>
<i>p</i>	<i>para</i>
Ph	Phenyl
PPA	Polyphosphoric acid
PPh ₃	Triphenylphosphine
Pyrr	Pyrrolidine
q	Quartet
rt	Room temperature
s	Singlet
SM	Starting material
S _N 2	bimolecular nucleophilic substitution
t	Triplet
TBHP	<i>tert</i> -butylhydroperoxide
<i>t</i> -Bu	tertiary butyl
<i>t</i> -BuOK	Potassium <i>tert</i> -butoxide

TEOF	Triethyl orthoformate
TFE	2,2,2-trifluoroethanol
TfOH	Trifluoromethanesulfonic acid
TLC	Thin layer chromatography
TMOF	Trimethyl orthoformate
TMS	Trimethylsilane
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
Ts	Tosyl
TsOH.H ₂ O	<i>para</i> -Toluenesulfonic acid monohydrate
UV	Ultraviolet

Contents

1	Introduction	19
1.1	Structure and properties of hypervalent iodine(III)	19
1.2	Iodine(III) mediated ring contraction of 1,2-dihydronaphthalenes	21
1.3	Asymmetric reactions mediated by hypervalent iodine(III)	29
2	Objectives	43
3	Results and discussion	44
3.1	Preparation of substrates	44
3.1.1	Preparation of cyclic olefinic substrates via a reduction/dehydration protocol	44
3.1.2	Preparation of ketone precursors for reduction/dehydration	48
3.1.3	Preparation of trisubstituted olefinic substrates via Grignard protocol	58
3.1.4	Preparation of protected amine tetralones	60
3.1.5	Preparation of phenolic substrates via demethylation of methyl ethers	62
3.1.6	Preparation of acetyl and benzoyl protected olefinic substrates	63
3.1.7	Preparation benzo-methylene 139 via Wittig reaction	65
3.1.8	Summary of the prepared cyclic olefins	67
3.1.9	Synthesis of chiral iodoarene compounds	68
3.2	Ring contraction reaction mediated by HTIB	76
3.2.1	Oxidation of 2 <i>H</i> -chromenes and 2,3-dihydrobenzo[<i>b</i>]oxepines with iodine(III)	76
3.2.2	Synthesis of functionalized indanes with HTIB	90
3.2.3	Oxidative rearrangement of alkenes using <i>in situ</i> generated hypervalent iodine(III)	99
3.3	Asymmetric Ring contraction reaction mediated by chiral iodine(III)	106
4	Conclusion	115
5	Experimental Section	117
5.1	Preparation of cyclic olefinic substrates	117
5.2	Synthesis of chiral iodoarene compounds	148
5.3	Oxidation of cyclic alkenes mediated by HTIB	154
5.4	<i>In situ</i> generation of HTIB for oxidative rearrangement	182
5.5	Asymmetric ring contraction reactions mediated by chiral I(III)	187
6	NMR Spectra, HPLC and GC Chromatograms	201
7	References	421
8	Curriculum Vitae	427

Table of Contents

1	Introduction	19
1.1	Structure and properties of hypervalent iodine(III)	19
1.2	Iodine(III) mediated ring contraction of 1,2-dihydronaphthalenes	21
1.3	Asymmetric reactions mediated by hypervalent iodine(III)	29
2	Objectives	43
3	Results and discussion	44
3.1	Preparation of substrates	44
3.1.1	Preparation of cyclic olefinic substrates via a reduction/dehydration protocol	44
3.1.2	Preparation of ketone precursors for reduction/dehydration	48
3.1.3	Preparation of trisubstituted olefinic substrates via Grignard protocol	58
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3.2	Ring contraction reactions mediated by HTIB	76
3.2.1	Oxidation of 2 <i>H</i> -chromenes and 2,3-dihydrobenzo[<i>b</i>]oxepines with iodine(III)	76
3.2.2	Synthesis of functionalized indanes with HTIB	90
3.2.3	Oxidative rearrangement of alkenes using <i>in situ</i> generated hypervalent iodine(III)	99
3.3	Asymmetric Ring contraction reactions mediated by chiral iodine(III)	106
4	Conclusion	115
5	Experimental Section	117
5.1	Preparation of cyclic olefinic substrates	117
5.1.1	1,2-Dihydronaphthalene (1a): General procedure reduction/dehydration	117
5.1.2	1-Methyl-1,2-dihydronaphthalene (1b)	118
5.1.3	4-(3,4-Dichlorophenyl)-3,4-dihydronaphthalen-1(2 <i>H</i>)-one (85f)	119
5.1.4	1-(3,4-Dichlorophenyl)-1,2-dihydronaphthalene (1f)	120
5.1.5	6,7-Dihydro-5 <i>H</i> -benzo[7]annulene (87a)	121
5.1.6	2 <i>H</i> -Chromene (1g)	121
5.1.7	2 <i>H</i> -Thiochromene (1s)	122
5.1.8	2-(3-Methylbut-2-enyl)phenol (98)	123
5.1.9	2,2-Dimethyl-2 <i>H</i> -chromene (1h) and 2-(prop-1-en-2-yl)-2,3-dihydrobenzofuran (99)	123
5.1.10	2,3-Dihydro-2,2-dimethylchromen-4-one (85h)	124
5.1.11	2,2-Dimethyl-2 <i>H</i> -chromene (1h)	124
5.1.12	4-Phenoxy butanoic acid (116)	125
5.1.13	3,4-Dihydrobenzo[<i>b</i>]oxepin-5(2 <i>H</i>)-one (86b)	126
5.1.14	2,3-Dihydrobenzo[<i>b</i>]oxepine (87b)	126
5.1.15	4-Methyl-1,2-dihydronaphthalene (1aa): General procedure Grignard protocol	127
5.1.16	4-Methyl-2 <i>H</i> -1-benzopyran (1gg)	128
5.1.17	2,3-Dihydro-5-methylbenzo[<i>b</i>]oxepine (87bb)	128
5.1.18	2,2,4-Trimethyl-2 <i>H</i> -chromene (1hh)	129
5.1.19	2,3-Dihydro-2-phenylchromen-4-one (85q)	129
5.1.20	2,3-Dihydro-2-phenylquinolin-4(1 <i>H</i>)-one (130)	130
5.1.21	1-Acetyl-2,3-dihydro-2-phenylquinolin-4(1 <i>H</i>)-one (85r)	131
5.1.22	<i>N</i> -(5-Oxo-5,6,7,8-tetrahydronaphthalen-2-yl)acetamide (85l)	131
5.1.23	<i>N</i> -(7,8-Dihydronaphthalen-2-yl)acetamide (1l)	132
5.1.24	<i>N</i> -(5-Oxo-5,6,7,8-tetrahydronaphthalen-2-yl)benzamide(85m)	133
5.1.25	<i>N</i> -(7,8-Dihydronaphthalen-2-yl)benzamide (1m)	133
5.1.26	4-Methyl- <i>N</i> -(5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)benzenesulfonamide (85n)	134
5.1.27	<i>N</i> -(7,8-dihydronaphthalen-2-yl)-4-methylbenzenesulfonamide (1n)	135
5.1.28	(9 <i>H</i> -Fluoren-9-yl)methyl (5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)carbamate (85o)	136
5.1.29	(9 <i>H</i> -Fluoren-9-yl)methyl (7,8-dihydronaphthalen-2-yl)carbamate (1o)	137
5.1.30	7-Nitro-3,4-dihydronaphthalen-1(2 <i>H</i>)-one (117) and 5-nitro-3,4-dihydronaphthalen-1(2 <i>H</i>)-one (118)	138
5.1.31	7-Amino-1,2,3,4-tetrahydronaphthalen-1-ol (119) and 7-amino-1,2,3,4-tetrahydronaphthalen-1-ol (120)	138
5.1.32	<i>N</i> -(8-Oxo-5,6,7,8-tetrahydronaphthalen-2-yl)acetamide (85p)	139
5.1.33	<i>N</i> -(5,6-Dihydronaphthalen-2-yl)acetamide (1p)	140
5.1.34	7,8-Dihydronaphthalen-1-ol (88j)	141
5.1.35	7,8-Dihydronaphthalen-1-yl acetate (138j)	141
5.1.36	7,8-Dihydronaphthalen-1-yl benzoate (138s)	142
5.1.37	7-Methoxy-1,2-dihydronaphthalene (1k)	143
5.1.38	7,8-Dihydronaphthalen-2-ol (88k)	143
5.1.39	7,8-Dihydronaphthalen-2-yl acetate (138k)	144

5.1.40	6-Methoxy-1,2-dihydronaphthalene (1c)	145
5.1.41	5,6-Dihydronaphthalen-2-ol (88c)	145
5.1.42	5,6-Dihydronaphthalen-2-yl acetate (138c)	146
5.1.43	1-Methylene-1,2,3,4-tetrahydronaphthalene (139)	147
5.2	Synthesis of chiral iodoarene compounds	148
5.2.1	(<i>R</i>)-Ethyl 2-(2-iodophenoxy)propanoate (36m)	148
5.2.2	(<i>R</i>)-2-(2-Iodophenoxy)propanoic acid (36s)	148
5.2.3	(2 <i>R</i>)-(1 <i>R</i> ,2 <i>S</i> ,5 <i>R</i>)-2-Isopropyl-5-methylcyclohexyl 2-(2-iodophenoxy)propanoate (36p)	149
5.2.4	(<i>R</i>)-2-(2-Iodophenoxy)- <i>N</i> -phenylpropanamide (36q)	149
5.2.5	(<i>R</i>)-2-(2-Iodophenoxy)- <i>N</i> -(2,6-dimethylphenyl)propanamide (36r)	150
5.2.6	(1 <i>R</i> ,2 <i>S</i> ,5 <i>R</i>)-2-isopropyl-5-methylcyclohexyl 2-iodobenzoate (36o)	151
5.2.7	2-Iodobenzene-1,3-diol (34)	151
5.2.8	Diethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))-(2 <i>R</i> ,2' <i>R</i>)-dipropionate ((<i>R</i> , <i>R</i>)- 36a)	152
5.2.9	Diethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))-(2 <i>S</i> ,2' <i>S</i>)-dipropionate ((<i>S</i> , <i>S</i>)- 36a)	153
5.2.10	(2 <i>R</i> ,2' <i>R</i>)-2,2'-((2-iodo-1,3-phenylene)bis(oxy))dipropionic acid (36b)	153
5.2.11	(2 <i>R</i> ,2' <i>R</i>)-2,2'-((2-iodo-1,3-phenylene)bis(oxy))bis(<i>N</i> -mesitylpropanamide) (36i)	154
5.3	Oxidation of cyclic alkenes mediated by HTIB	154
5.3.1	4-Methoxy-4 <i>H</i> -chromene (174g) and <i>trans</i> -3,4-dimethoxy-3,4-dihydro-2 <i>H</i> -chromene (175g)	154
5.3.2	4-Methoxy-4 <i>H</i> -chromene (174g) and <i>trans</i> -3,4-Dimethoxy-3,4-dihydro-2 <i>H</i> -chromene (175g)	156
5.3.3	4-Methoxy-4 <i>H</i> -chromene (174g) and <i>trans</i> -3,4-Dimethoxy-3,4-dihydro-2 <i>H</i> -chromene (175g)	156
5.3.4	4-Ethoxy-4 <i>H</i> -chromene (176g) and <i>trans</i> -3,4-Diethoxy-3,4-dihydro-2 <i>H</i> -chromene (177g)	157
5.3.5	4-(2,2,2-Trifluoroethoxy)-4 <i>H</i> -chromene (178g)	158
5.3.6	4-(2,2,2-Trifluoroethoxy)-4 <i>H</i> -chromene (178g)	159
5.3.7	4-Methoxy-4 <i>H</i> -thiochromene (183i)	160
5.3.8	4-Methoxy-4 <i>H</i> -thiochromene (183i)	160
5.3.9	4-Ethoxy-4 <i>H</i> -thiochromene (184i)	161
5.3.10	<i>cis</i> -3,4-Dimethoxy-4-methyl-3,4-dihydro-2 <i>H</i> -chromene (185gg)	161
5.3.11	<i>cis</i> -3,4-Dihydro-3,4-dimethoxy-4-methyl-2 <i>H</i> -chromene (185gg)	162
5.3.12	<i>cis</i> -3,4-Diethoxy-4-methyl-3,4-dihydro-2 <i>H</i> -chromene (186gg)	162
5.3.13	4-(Bis(2,2,2-trifluoroethoxy)methyl)chromane (190b)	163
5.3.14	4-(Dimethoxymethyl)chromane (194b)	164
5.3.15	(3,4-Dihydro-2 <i>H</i> -chromen-4-yl)methanol (191b) and chroman-4-ylmethylene bis(4-methylbenzenesulfonate) (192b)	165
5.3.16	Chroman-4-ylmethylene bis(4-methylbenzenesulfonate) (192b)	166
5.3.17	1-(3,4-Dihydro-2 <i>H</i> -chromen-4-yl)ethanone (195bb)	166
5.3.18	(2,2-Dimethyl-2,3-dihydrobenzofuran-3-yl)methanol (200h)	167
5.3.19	3-(Dimethoxymethyl)-2,2-dimethyl-2,3-dihydrobenzofuran (201h)	168
5.3.20	1-(2,2-Dimethyl-2,3-dihydrobenzofuran-3-yl)ethanone (202hh)	169
5.3.21	1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1 <i>H</i> -indene (16a)	169
5.3.22	<i>N</i> -(1-(Dimethoxymethyl)-2,3-dihydro-1 <i>H</i> -inden-5-yl)acetamide (7l)	170
5.3.23	Reaction of <i>N</i> -(7,8-dihydronaphthalen-2-yl)-4-methylbenzenesulfonamide (1n) with HTIB	171
5.3.24	1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1 <i>H</i> -inden-4-yl acetate (16j)	172
5.3.25	1-(bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1 <i>H</i> -inden-5-yl acetate (16k)	173
5.3.26	3-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1 <i>H</i> -inden-5-yl acetate (16c)	173
5.3.27	<i>N</i> -(1-(Dimethoxymethyl)-2,3-dihydro-1 <i>H</i> -inden-5-yl)benzamide (7m)	174
5.3.28	(9 <i>H</i> -Fluoren-9-yl)methyl (1-(dimethoxymethyl)-2,3-dihydro-1 <i>H</i> -inden-5-yl)carbamate (7o)	175
5.3.29	1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1 <i>H</i> -inden-4-yl benzoate (16s)	176
5.3.30	(1 <i>R</i> ,3 <i>S</i>)-1-(bis(2,2,2-trifluoroethoxy)methyl)-3-(3,4-dichlorophenyl)-2,3-dihydro-1 <i>H</i> -indene (16f)	176
5.3.31	((1 <i>R</i> ,3 <i>R</i>)-3-(3,4-Dichlorophenyl)-2,3-dihydro-1 <i>H</i> -inden-1-yl)methanol (17f)	177
5.3.32	(1 <i>R</i> ,3 <i>S</i>)-1-(3,4-Dichlorophenyl)-3-(dimethoxymethyl)-2,3-dihydro-1 <i>H</i> -indene (7f)	178
5.3.33	(1 <i>R</i> ,3 <i>R</i>)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-3-methyl-2,3-dihydro-1 <i>H</i> -indene (16b)	179
5.3.34	(1 <i>R</i> ,3 <i>R</i>)-1-(Dimethoxymethyl)-3-methyl-2,3-dihydro-1 <i>H</i> -indene (7b)	179
5.3.35	((1 <i>R</i> ,3 <i>S</i>)-3-Methyl-2,3-dihydro-1 <i>H</i> -inden-1-yl)methanol (17b)	180
5.3.36	(1,2,3,4-Tetrahydronaphthalen-1-yl)methanol (191a)	180
5.3.37	(2,3-Dihydro-1 <i>H</i> -inden-1-yl)methanol (17a)	181
5.4	<i>In situ</i> generation of HTIB for oxidative rearrangement	182
5.4.1	(1,2,3,4-Tetrahydronaphthalen-4-yl)methanol (191a). General Procedure A: <i>In situ</i> generation of HTIB for oxidative rearrangement of alkenes followed by reduction with NaBH ₄	182
5.4.2	(3,4-Dihydro-2 <i>H</i> -chromen-4-yl)methanol (191b)	182
5.4.3	(2,3-Dihydro-1 <i>H</i> -inden-1-yl)methanol (17a)	183
5.4.4	8,9-Dihydro-5 <i>H</i> -benzo[7]annulen-6(7 <i>H</i>)-one (216). General Procedure B: <i>In situ</i> generation of HTIB for oxidative rearrangement of alkenes	183
5.4.5	1-Phenylpropan-2-one (218)	184
5.4.6	1-(1,2,3,4-Tetrahydronaphthalen-4-yl)ethanone (195aa). General Procedure C: <i>In situ</i> generation of HTIB for ring contraction of methyl substituted cyclic alkenes	185
5.4.7	1-(3,4-Dihydro-2 <i>H</i> -chromen-4-yl)ethanone (195bb)	185

5.4.8	1-(2,3-Dihydro-1 <i>H</i> -inden-1-yl)ethanone (15aa)	186
5.4.9	1-Methyl-2-tetralone (209aa).....	186
5.4.10	Reaction of 6,7-dihydro-5 <i>H</i> -benzo[7]annulene (191a) with <i>In situ</i> generation of Iodine(III) from <i>p</i> -C ₆ H ₄ I ₂ ...	187
5.5	Asymmetric ring contraction reactions mediated by chiral I(III)	187
5.5.1	(<i>R</i>)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1 <i>H</i> -indene (16a).....	187
5.5.2	(<i>R</i>)-(2,3-Dihydro-1 <i>H</i> -inden-1-yl)methanol (17a).....	188
5.5.3	(<i>R</i>)- <i>N</i> -(1-(Dimethoxymethyl)-2,3-dihydro-1 <i>H</i> -inden-5-yl)acetamide (7l)	189
5.5.4	(<i>R</i>)- <i>N</i> -(1-(Dimethoxymethyl)-2,3-dihydro-1 <i>H</i> -inden-5-yl)benzamide (7m)	189
5.5.5	(9 <i>H</i> -Fluoren-9-yl)methyl (<i>R</i>)-(1-(dimethoxymethyl)-2,3-dihydro-1 <i>H</i> -inden-5-yl)carbamate (7o).....	190
5.5.6	(<i>R</i>)- <i>N</i> -(1-(Dimethoxymethyl)-2,3-dihydro-1 <i>H</i> -inden-5-yl)acetamide (7l)	191
5.5.7	(<i>R</i>)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1 <i>H</i> -inden-4-yl acetate (16j)	192
5.5.8	(<i>R</i>)-1-(bis(2,2,2-Trifluoroethoxy)methyl)-2,3-dihydro-1 <i>H</i> -inden-5-yl acetate (16k).....	192
5.5.9	(<i>R</i>)-3-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1 <i>H</i> -inden-5-yl acetate (16c).....	193
5.5.10	(<i>R</i>)-1-(bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1 <i>H</i> -inden-4-yl benzoate (16s).....	194
5.5.11	(<i>R</i>)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1 <i>H</i> -inden-4-yl acetate(16j)	194
5.5.12	(1 <i>S</i> ,3 <i>R</i>)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-3-(3,4-dichlorophenyl)-2,3-dihydro-1 <i>H</i> -indene (16f) and ((1 <i>R</i> ,3 <i>R</i>)-3-(3,4-dichlorophenyl)-2,3-dihydro-1 <i>H</i> -inden-1-yl)methanol (17f).....	195
5.5.13	(1 <i>R</i> ,3 <i>S</i>)-1-(3,4-Dichlorophenyl)-3-(dimethoxymethyl)-2,3-dihydro-1 <i>H</i> -indene (7f)	196
5.5.14	(1 <i>S</i> ,3 <i>S</i>)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-3-methyl-2,3-dihydro-1 <i>H</i> -indene (16b) and ((1 <i>R</i> ,3 <i>S</i>)-3-methyl- 2,3-dihydro-1 <i>H</i> -inden-1-yl)methanol (17b)	197
5.5.15	(1 <i>S</i> ,3 <i>S</i>)-1-(Dimethoxymethyl)-3-methyl-2,3-dihydro-1 <i>H</i> -indene (7b).....	198
5.5.16	(<i>S</i>)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1 <i>H</i> -indene (16a)	199
5.5.17	(<i>S</i>)-1-(bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1 <i>H</i> -indene (16a)	199
5.5.18	(<i>S</i>)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1 <i>H</i> -indene (16a)	200
6	NMR Spectra, HPLC and GC Chromatograms	201
7	References	421
8	Curriculum Vitae	427

1 Introduction

1.1 Structure and properties of hypervalent iodine(III)

The discovery of hypervalent iodine reagents has been made long time ago. Dichloro iodo benzene, the first member of this class was reported by Willgerodt in 1886. “Hypervalent” refers to a main group element that breaks the octet rule and formally has more than eight electrons in its valence shell. Similarly the word iodane is given to hydrogen iodide (HI), a colorless non-flammable gas.^{1,2} Compounds with nonstandard bonding number are presented by the lambda notation as per IUPAC rules and guidelines, thus H_3I is denoted as λ_3 -iodane and H_5I as λ_5 -iodane. Hypervalent iodine(III) compounds (ArIL_2) (L: heteroatom ligand) have geometry of a pseudotrigonal bipyramid. The least electronegative groups generally an aryl group and lone pairs of electrons occupy equatorial positions and two heteroatom ligands (L), the most electronegative stay in apical positions (**Figure 1a**). The linear hypervalent iodine bond (L-I-L) bond in T-shaped structure which is weaker than normal covalent bond is a three-center four electron bond (3c-4e bond) with two electrons from the doubly occupied 5p orbital on iodine and one electron from each of the epical ligand (L). Whereas the Ar-I σ -bond is formed by a normal two-electron covalent bond with 5sp^2 hybridization.¹

Figure 1. a) Pseudotrigonal bipyramid geometry. b) Orbitals in hypervalent iodine(III)

The two lower energy bonding and nonbonding molecular orbitals of the hypervalent 3c–4e bond are filled. As the filled nonbonding molecular orbital, which is located on apical ligands has a node at the central iodine atom, develops partial positive charge on iodine while partial negative charge develop on the heteroatom ligands in axial position. The partial positive charge on the iodine of the highly polarized 3c–4e bond makes the I(III) an electrophilic agent (**Figure 1b**).¹

The chemistry of hypervalent iodine(III) is based on the strongly electrophilic nature of the iodine making it susceptible to nucleophilic attack, in combination with the leaving group ability of phenyliodonio group. The hypervalent I(III) reagents reacts via two main modes: a) ligand exchange; b) reductive elimination. The two heteroatoms ligands are good leaving groups which is an essential feature in ligand exchange and in reductive elimination.¹

Ligand exchange is involved in external nucleophiles displacement of the heteroatom ligands of λ_3 -iodanes with no change in the oxidation state at iodine(III) centre. The ligand exchange occurs by two mechanistic pathways, i.e. associative and dissociative. When compared to associative mechanism, dissociative pathway seems unreasonable and can be turn down due to the dicoordinated [8-I-2] iodonium ion which is considered highly energetic species.

Figure 2. Ligand exchange pathways

The associative pathway is better explained in **Figure 2**. The nucleophile reacts with the electrophilic iodine atom of ArIL_2 [10-I-3] through the C-I σ^* orbital resulting in the formation

of a *trans*-tetracoordinated [12-I-4] iodate intermediate with a square-planar geometry. The isomerization of *trans*-iodate to a *cis*-iodate counterpart followed by the elimination of a heteroatom ligand L from the tetracoordinated specie gives aryl- λ_3 -iodane ArI(Nu)L [10-I-3] as shown. The overall process can be summarized as an exchange of a heteroatom ligand on iodine(III) with a nucleophile via addition-elimination sequence.

Reductive Elimination is a process by which a “super-leaving group” (hypernucleofuge) reduces the hypervalent atom to the normal valency with octet structure. This process is very facile and energetically feasible and mostly proceeds without the assistance of an added reagent. This process is favorable by entropy, as one hypervalent species decomposes into three components (**Figure 3**).

Figure 3. Reductive Elimination pathway

1.2 Iodine(III) mediated ring contraction of 1,2-dihydronaphthalenes

In last decade the literature bears witness to the tremendous advances in the field of hypervalent iodine chemistry.¹⁻⁶ Hypervalent iodine reagents play a substantial role in chemical synthesis, for example, carbon-carbon bond formations,⁷⁻¹³ rearrangements¹⁴⁻¹⁸ and functional group transformations.¹⁹⁻²¹ The ready availability, nontoxic profile and their high oxidation potential give them a superiority over toxic heavy metal-based oxidants, such as lead(IV), mercury(II) and thallium(III).¹⁻⁶ Among the hypervalent iodine species, [hydroxy(tosyloxy)iodo]benzene [HTIB or Koser's reagent]²² is important in metal-free processes that lead to a range of interesting and characteristic transformations such as rearrangement of alkenes²³ (including ring contraction²⁴⁻²⁸ and ring expansion^{29,30}), cyclopropanation,³¹ electrophilic cyclization,³² α -functionalization of carbonyl compounds,³³ tosyloxylation of aromatic rings³⁴ and oxidative biaryl couplings.³⁵

In synthetic organic chemistry, ring contraction reaction is a powerful method that converts simple molecular frameworks into complex ones. During the process, the product has ring size smaller than the substrate. This single step operation involves reorganization of the bonds, affording structures with different properties.^{4,24} For almost two decades, our group is being working on ring contraction reaction, specially in 1,2-dihydronaphthalenes mediated by oxidants, such as thallium(III) and hypervalent iodine(III).^{24,27,28,36,37}

The ring contraction reaction of iodoarene difluorides(III) with cyclic alkenes was first studied by Hara et al.³⁸ The reaction of 1,2-dihydronaphthalenes **1a** and **1aa** with *p*-iodotoluene difluoride (*p*-Tol-IF₂) in the presence of 5HF-Et₃N gave ring contraction fluorinated indanes **2a** and **2aa** respectively in good yields (**Scheme 1**).

Scheme 1

The proposed reaction mechanism is given below (**Scheme 2**).^{27,38} The attack of electrophilic iodotoluene difluoride activated by HF on double bond of the cyclic alkene **1a** followed by the addition of a fluoride ion from the opposite face gives intermediate **4**. The anti-periplanarity, required for the rearrangement, is accomplished by equilibration of adduct **4** to its more stable conformational isomer **5**. The reductive elimination step involves the migration of an aryl bond in anti-periplanar fashion giving ring contraction carbocation intermediate **6** stabilized by fluorine. The addition of the fluoride ion to the carbocation gives the ring contraction difluorinated product **2a**.

Scheme 2. Mechanism of the ring contraction

Recently, the ring contraction reaction mediated by HTIB in 1,2-dihydronaphthalene (**1a**) and its derivatives has been extensively studied in our group.^{27,28} The investigation started with the reaction of the cyclic alkene **1a** with HTIB in MeOH as solvent (Table 1). The ring contraction indane **7a** was obtained in 36% yield together with *trans*-**8a** and *cis*-**8a** addition products in 28 and 14% yields, respectively in MeOH at room temperature (entry 1). The reaction of 1-methyl-1,2-dihydronaphthalene (**1b**) gave *trans*-indane **7b** as major product along with addition *trans* and *cis*-products **8b** (entry 2). Substrate **1c** bearing methoxy group at the aromatic ring gave desired indane **7c** in low yield (3%) along with *trans*-**8c** and *cis*-**8c** addition product in 26% and 17% yields, respectively (entry 3). However when tri-substituted cyclic alkene **1aa** was subjected to similar reaction conditions only addition products *trans*- and *cis*-**8aa** were isolated (entry 4).

Table 1. Oxidation of 1,2-dihydronaphthalenes with HTIB in MeOH at rt.

Entry	Substrate	Conditions	Product (Yield) ^a
1		1.0 equiv HTIB 2 h	(36%) + (28%) + (14%)
2		1.2 equiv HTIB 30 min	(55%) + + (12%) <i>trans:cis, 4:3</i>
3		1.2 equiv HTIB 1 h	(3%) + (26%) + (17%) <i>trans-8c</i> (26%) <i>cis-8c</i> (17%)
4		1.0 equiv HTIB 1 h	(60%) + (31%) <i>trans-8aa</i> (60%) <i>cis-8aa</i> (31%)

a) isolated yield

The selective formation of the *trans*-indane acetal **7b** can be explained by the ring contraction mechanism given below (**Scheme 3**). The HTIB makes electrophilic attack upon the double bond of cyclic alkene **1b** from the opposite side of the remote methyl group giving benzylic carbocation **9**. The presence of electron donating group *para* (position 7) to migrating carbon (position 4a) could further stabilize carbocation **9** by mesomeric effect. The nucleophilic attack of MeOH gives *anti*-addition intermediate **10**. The necessary *anti*-periplanarity for the rearrangement is achieved via equilibration to its more stable conformational isomer **11**. Migration of the aryl group on **12** gives the oxonium **13**. Finally, addition of MeOH leads to desired *trans*-acetal product **7b**.

Scheme 3. Mechanism of the formation of *trans*-ring contraction product **7b**

Using acetonitrile (ACN) as solvent, naphthalene (**14a**) was obtained in 30% yield when alkene **1a** was treated with HTIB (Table 2, entry 1). Only the ring contraction keto-indane **15aa** was isolated when 1-methyl substituted alkene **1aa** was subjected to reaction condition (entry 2). It should be noted here that exclusive formation of addition products were observed in MeOH for the above mentioned substrate **1aa** (Table 1, entry 4). Similarly, tri-substituted alkene **1d** furnished *trans*-ring contraction product **15d** in good yield (entry 3).^{27,28}

Table 2. Oxidation of 1,2-dihydronaphthalenes with 1.2 equiv HTIB in ACN with molecular sieves 3 Å at 0 °C for 10 min

Entry	Substrate	Product
1	1a	14a (30%)
2	1aa	15aa (51%)
3	1d	15d (60%) <i>trans:cis</i> = 10:1

Fluoroalcohols, like TFE and HFIP, exhibit unique properties like high polarity, low nucleophilicity, high ionizing power and exceptional hydrogen-bond donor ability. Moreover, TFE and HFIP have the capability to stabilize reactive cationic intermediates which are produced by the action of hypervalent iodine species.³⁹ Fluoroalcohols, like TFE⁴⁰⁻⁴² and HFIP⁴³⁻⁴⁵ have been successfully used as solvents in several reactions with hypervalent iodine compounds. The ring contraction reaction was also studied in these high polar low nucleophilic solvents aiming the suppression of byproducts formation.²⁷ The yield for the ring contraction product **16a** of alkene **1a** in TFE increased almost to the double (73%) (Table 3, entry 1) when compared to the reaction carried out in MeOH (36%) with I(III) (Table 1, entry 1). The reaction of 1-methyl substituted alkene **1b** with HTIB in TFE led to acetal indane **16b** in greater yield (70%) than in MeOH (55%). However, when compared to reaction in MeOH the diastereoselectivity of the reaction in TFE is lower (Table 1 and Table 3, entry 2). The tri-substituted alkene **1aa** with HTIB in TFE afforded ring contraction indane **15aa** in higher yield than using acetonitrile (72% vs 51%). Alkene **1d** also gave ring contraction product **15d** in higher yield but in lower diastereoselectivity than in acetonitrile (Table 2, entry 3 and Table 3, entry 4). The oxidation reaction of substrate **1a** with HTIB in more polar solvent HFIP resulted

in ring contraction aldehyde which was reduced *in situ* to hydroxyl functionalized indane **17a** in 74% yield (entry 5).

Table 3. Reaction of 1,2-dihydronaphthalenes with 1.1 equiv HTIB in fluoroalcohols at 0 °C for 5 min

Entry	Substrate	Conditions	Product
1		TFE	16a (73%)
2		TFE	16b (70%) <i>trans:cis</i> = 5:1
3		TFE	15aa (72%)
4		TFE/DCM (1:4)	15d (76%) <i>trans:cis</i> = 7:1
5		a) HFIP/DCM (1:4) b) 5 equiv NaBH ₄ , rt, 2 h	17a (74%)

In summary, by changing the reaction conditions, different functionalized indanes can be obtained. Using nucleophilic solvents, such as MeOH or TFE, an acetal indane can be obtained in moderate to good yields. However, using bulky HFIP resulted in the isolation of the corresponding aldehyde or can also be reduced *in situ* to give alcohol.

The iodine(III) mediated ring contraction methodology was efficiently applied in the total syntheses of the sesquiterpenes (–)- and (+)-mutisianthol (**18**) (**Scheme 4**). The target molecules exhibit moderate activity against human cancer cell lines SF-295, HCT-8, and MDA-MB-435.⁴⁶

Scheme 4. Ring contraction approach for the total synthesis of (-)-mutisianthol (**18**)

The use of indatraline (**19**) in the treatment of drug abuse has been investigated. A diastereoselective ring contraction of a 1,2-dihydronaphthalene promoted by HTIB was a key step in the synthesis of (±)-indatraline (**Scheme 5**).^{28,47}

Scheme 5. Ring contraction approach for the total synthesis of (±)-indatraline (**19**)

1.3 Asymmetric reactions mediated by hypervalent iodine(III)

The advent of chiral hypervalent iodine reagents enabled scientists to accomplish a number of important organic transformations in enantioselective fashion, such as α -arylation of carbonyl compound,⁴⁸ the dearomatization spirolactonization of naphthols,^{40,49} oxidative cycloetherification,⁵⁰ diamination of styrenes⁵¹ and oxyamination.⁵²

The first chiral hypervalent iodine reagent (diphenyliodonium tartrate) was discovered in 1907.⁵³ However, its potential as reagents in asymmetric oxidative protocols have only been recognized over the last decade. The groundbreaking work was done by Imamoto et al. in 1986.⁵⁴ They prepared chiral iodine(III) reagents (*R,R*)-**22a–22c** *in situ* by reacting iodosylbenzene (**21**) with various (*R,R*)-tartaric anhydrides **20a–20c** in acetone at room temperature followed by the addition of sulfides **23**. The optically active sulfoxides **24** were obtained in moderate to good yield and up to 53% *ee* (**Scheme 6**).

Scheme 6. Asymmetric oxidations of sulfides to sulfoxides

In 1990, Koser and coworkers⁵⁵ synthesized two new chiral I(III) reagents, (+) or (–)-**27**, through a ligand exchange reaction between (1*S*,2*R*,5*S*)-(+) or (1*R*,2*S*,5*R*)-(–)-menthol (**26**) and the iodine(III) derivative **25** in excellent yields. These menthol derived chiral reagents (+) or (–)-**27** were treated with various sulfides **23** which gave mixtures of diastereomers (+) or (–)-**28** in high yields and up to 57% d.e. Separation by recrystallization of major diastereomers

followed by basic hydrolysis resulted in chiral sulfoxides (*S*) or (*R*)-**24** in good to high *ee* (**Scheme 7**).

Scheme 7. Asymmetric oxidations of sulfides to sulfoxides

In 2008, Dohi et al. reported the first enantioselective dearomatization of phenols using chiral hypervalent iodine(III) reagent.⁴⁰ A promising new chiral hypervalent iodine(III) reagent *R*-(**30**), derived from rigid spirobiindane backbone, was synthesized for the purpose. 4-Substituted- α -naphthols derivatives **29a-29d** gave effectively *o*-spirolactonization products **31a-31d** in good enantioselectivities and yields. One exception is 4-methoxy substituted **29e**, which gave racemic product **31e** in low yield (**Scheme 8**).

Scheme 8. *o*-Spirolactonization of α -naphthols mediated by chiral iodine(III)

This reaction could either proceed through an associative (**A**) pathway “intramolecular S_N2’ type displacement” or by a dissociative (**B**) one, which involves nucleophilic attack on carbocation (**Scheme 9**).

Scheme 9. Plausible reaction mechanisms of spirolactonization of phenol

After screening different solvents it was observed that highest levels of asymmetric induction could be achieved only if the reaction is carried out in nonpolar and moderately polar solvents (Table 4). Those observations were consistent with an associative mechanism (**A**).

Table 4: Correlation of the solvent polarity and *ee* values for the reaction

Entry	$E_T(30)$ [kcalmol ⁻¹]	% <i>ee</i>	%Yield
1	CCl ₄ [32.5]	72	47
2	CHCl ₃ [39.1]	72	64
3	DCM[40.1]	59	65
4	ClCH ₂ CH ₂ Cl[41.9]	60	69
5	ACN[46.0]	20	50
6	ACN/AcOH (10:1)[46.5]	16	77
7	HFIP[69.3]	0	87

In 2010, Ishihara and co-workers designed and prepared a series of *C*₂-symmetric, conformationally flexible chiral aryl iodide(III) catalysts (**36a-36l**) derived from (–)-ethyl lactate using Mitsunobu protocol followed by hydrolysis and amidation reactions (**Scheme 10**).⁴⁹

Scheme 10. Synthesis of chiral iodoarenes

Chiral iodine(III) species obtained *in situ* upon reaction of *m*CPBA with aryl iodide **36i** induces spirocyclization reaction, with improved enantioselectivities and with a broader substrate scope when compared to results obtained by Dohi et al.⁴⁰ 1-Naphthol derivatives (**37a**, **37e-37j**) were treated with chiral aryl iodide **36i** (10 mol%) and *m*CPBA (1.2–1.5 equiv) under the optimized conditions. The oxidation of 4-substituted naphthol derivatives **37a** and **37f-37j** (bearing electron-donating or withdrawing groups) gave the corresponding spiro lactones **38a** and **38f-38j** in good to high yields with high enantioselectivities. Again the oxidation of 4-

methoxynaphthol derivative **37e** gave racemic product **38e** similar to that reported by Dohi et al.⁴⁰ (Scheme 11).

Scheme 11. Asymmetric spirolactonization of α -naphthols mediated by chiral iodine(III)

Kita et al. in 2013 came up with improved enantioselectivity (up to 92% *ee*) of spirolactonization products using a new pre-catalyst (*R*)-**39** derived from spirobiindane bearing *o*-ethyl substituents. After the assignment of absolute configuration of the lactone product as *R* they proposed a plausible transition state model to explain the observed configuration.⁵⁶ The oxidation of catalyst (*R*)-**39** by *m*CPBA gives the reactive iodine(III) species (*R*)-**40**. The apical approach of phenolic OH group of naphthol **37a** to the iodine(III) atom of the ring of (*R*)-**40** occurs selectively from the less hindered face as the iodine groups block access to substrate **37a** from the major groove of the two spirobiindane planes and opposite apical position of the iodine(III) by forming an oxygen bridge. Thus, the ligand exchange of spirobiindane species (*R*)-**40** with the naphthol oxygen gives intermediate *R*-**41**. In the reductive elimination step, the preferential attack of the carboxylic acid at the ipso position of the naphthol ring from the

unshielded *Re*-face of substrate gives spirolactonization product **38a** with (*R*)-configuration (Scheme 12)

Scheme 12. Plausible reaction mechanism spirolactonization of α -naphthols

In 2010, Fujita et al. developed a new family of catalysts, **43** and **44** following the procedure reported by Ishihara et al.^{49,57} Oxidative oxylation reactions of *o*-alk-1-enylbenzoate derivatives (**42a-42d**) were studied with optically active hypervalent iodine(III) reagents (**43** and **44**) using boron trifluoride diethyl etherate ($\text{BF}_3 \cdot \text{OEt}_2$) as an activator in the presence of acetic acid employed as nucleophile in DCM as solvent. The oxylation proceeds with *endo*-selectivity in addition with high enantioselectivity, giving six membered lactone products (**45a-45d**) (Scheme 13).

Scheme 13. *Endo*-selective oxylation *o*-alk-1-enylbenzoates with I(III)

Electrophilic addition of the iodine(III) reagent activated by acid (TsOH or BF₃.OEt₂) to alkene **46** gives cyclic iodonium intermediate **47**. This alkene oxidation step involves an efficient differentiation of the prochiral face of the double bond through the chiral iodine(III) reagent. The iodonium(III) intermediate **47** undergoes regioselective ring opening in the benzylic position by nucleophile attack giving intermediate **48**. An intramolecular nucleophilic displacement of the iodine group by the carbonyl oxygen leads to oxonium intermediated **49** which finally results in dioxygenated product **50** (Scheme 14).⁵⁷

Scheme 14. Plausible mechanism of enantioselective oxylactonization with I(III)

In 2011, Muniz and co-workers extended the use of chiral hypervalent iodine(III) reagents for an intermolecular enantioselective diamination of styrenes.⁵¹ Among several chiral iodine(III) reagents screened, **44** was identified as the most suitable iodine(III) for the above mentioned enantioselective transformation. Under the mild optimized condition, a series of styrenes **51a-51i** with different substitution patterns including compounds with *para*, *meta* and *ortho* substitution were converted into the corresponding diamines **52a-52i** in moderate to good yields and high *ee* using I(III) reagent **44** as the oxidant and bismesylimide as the nitrogen source (**Scheme 15**).

Scheme 15. Enantioselective diamination of styrenes using chiral iodine(III)

The mechanism proposed for enantioselective diamination of styrenes is given below (**Scheme 16**).⁵¹ The electrophilic attack of I(III) on the *Re*-face of the double bond gives cyclic iodonium intermediate **54** stabilized by counter anion. The nucleophilic attack of the nitrogen anion produces the vicinal *anti*-iodo(III) amine intermediate **55**. Removal of ligand as acetic acid by protonolysis affords the ion pair **55**. As the direct *anti*-C-N bond formation would result in incorrect stereochemistry, an aziridinium intermediate **57** formation is suggested. The nucleophilic ring opening of aziridinium intermediate **58** gives the final product with *S*-configuration.

Scheme 16. Mechanism of enantioselective diamination of styrenes using chiral iodine(III)

Uyanik et al. in 2010 for the first time use chiral quaternary ammonium (hypo)iodite catalyst for asymmetric oxidative cycloetherification reaction.⁵⁰ This enantioselective oxidative cycloetherification involved the conversion of ketophenols **59a-59d** to 2-acyl-2,3-dihydrobenzofuran derivatives **61a-61d** using a C_2 -symmetric chiral binaphthyl based quaternary ammonium (hypo)iodite. The quaternary ammonium (hypo)iodite catalyst was generated *in situ* by reaction of ammonium iodide precatalyst with atom economical hydrogen peroxide or anhydrous *tert*-butylhydroperoxide (TBHP) as mild stoichiometric oxidants. After the examination of several precatalysts, the *N*-spiro type quaternary ammonium iodide **60** bearing bulky and electron deficient substituents ($\text{Ar} = 3,5\text{-}[\text{3,5-(CF}_3)_2\text{C}_6\text{H}_3]\text{C}_6\text{H}_3$) at the 3,3'-positions gave the best results. The summary of the enantioselective oxidative cyclization with several ketophenol derivatives **59a-59d** under optimized conditions are given in **Scheme 17**.

Scheme 17. Enantioselective oxidative cycloetherification of keto phenols

The reaction pathway is not fully understood so far. There are several possibilities postulated for the reaction mechanism (**Scheme 18**).⁵⁰ In first step enolate intermediate **63** or **64** might be generated with (hypo)iodite species. The intramolecular iodine transfer reaction of **63** possibly gives intermediate **65** or **66**. In the next step, enantiomerically enriched cycloetherification product **67** could be achieved either through intramolecular S_N2 addition of ammonium phenoxide of **65** or via reductive elimination of **66** with inversion or retention of stereochemistry. Similarly, intermediate **64** could also give cycloetherification product **67** in enantioselective fashion via intramolecular S_N2' reaction of ammonium phenoxide.

Scheme 18. Possible reaction pathways of enantioselective oxidative cycloetherification

In 2013, Wirth et al. studied the enantioselective rearrangement of chalcones using chiral I(III) reagent.⁴⁸ After screening several Lewis acids as activating agents for chiral reagent **69**, TMSOTf was found as the best activator. Working with a mixture of TFE and DCM the reaction compatibility with a wide range of substrates **68a-68e** was studied. α -Arylated ketones **70a-70e** were formed in good yields and enantiomeric excess. Both the yield and the enantioselectivity were found to be depended on the substitution at the aromatic ring (**Scheme 19**).

Scheme 19. I(III) mediated enantioselective rearrangement of chalcones

The mechanism of enantioselective oxidative rearrangement of chalcone is given below (**Scheme 20**). The electrophilic attack of chiral I(III) on the double bond of chalcone **71** gives intermediate **72**. This step is considered to differentiate between the prochiral faces of the double bond of alkene **71**. The nucleophilic attack on carbocation intermediate **72** gives intermediate **73**. The migration of the aryl substituent in stereoselective fashion in **73** and subsequent nucleophilic attack of the solvent gives desired product **75**.

Scheme 20. Plausible mechanism of enantioselective rearrangement of chalcones

They also reported the asymmetric ring contraction reaction of 1,2-dihydronaphthalenes using chiral iodine(III). The ring contraction product **16a** was obtained in 59% *ee* using mesitylamide based chiral hypervalent iodine reagent **69**, prepared in five steps from 2-iodoresorcinol (**34**) (**Scheme 21**). Under similar reaction condition *trans*-ring contraction product **7f** was isolated in 9% *ee*.⁴⁸ No absolute configuration was assigned to ring contraction products.

Scheme 21. Asymmetric ring contraction reaction mediated by I(III)

The examples shown in this section demonstrate the great potential of hypervalent iodine reagents in synthetic organic chemistry. A number of important metal free transformations can be carried out using chiral hypervalent iodine reagents. Similarly ongoing research is unveiling the structural requirements, such as design, rigidity/flexibility and

symmetry, together with mechanistic studies for successful reagents and catalysts. The exploration of these reagents and catalysts is a fruitful area and will certainly lead to exciting developments in chemical synthesis.

2 Objectives

There are three principal objectives behind our work. First one aims to examine the behavior of 2*H*-chromenes and its derivatives with I(III) reagents to obtain functionalized 2,3-dihydrobenzofurans and its derivatives via ring contraction reaction. After development, the methodology could also be extended towards the total synthesis of natural products containing benzofurans core skeleton (**Scheme 22**).

Second aim is the development of a flexible and general strategy for oxidative rearrangement reactions using *in situ* generated iodine(III) species from inexpensive reagents (**Scheme 23**).

Finally, we also intend to explore the asymmetric ring contraction by using chiral iodine(III) in various cyclic alkenes. The idea is to make the attack of chiral iodine(III) selectively either on *Re* or *Si* face to get enantioenriched functionalized indanes (**Scheme 24**).

Scheme 24

3 Results and discussion

3.1 Preparation of substrates

3.1.1 Preparation of cyclic olefinic substrates via a reduction/dehydration protocol

Several cyclic olefinic substrates have been synthesized via reduction/dehydration protocol to study the oxidative rearrangement reaction with iodine(III) under the racemic and asymmetric conditions. The commercially available α -tetralone (**85a**) was reduced with NaBH₄ in THF/EtOH to the corresponding alcohol in 97% yield as a white solid. Dehydration of alcohol at 130 °C in the presence of catalytic amount of *p*-toluene sulfonic acid (TsOH.H₂O) in toluene gave desired alkene **1a** in 87% yield (Table 5, entry 1).^{27,28} 4-Aryl and methyl substituted alkenes **1b** and **1f** were synthesized from tetralones **85b** and **85f** under similar conditions in 92% and 91% yields, respectively (entries 2 and 3).^{27,28} In a similar fashion, seven-membered ring substrate **87a** was prepared from 1-benzosuberone (**86a**) in 92% yield (entry 4).²⁷ 2*H*-Chromenes (**1g** and **1h**) and thiochromene **1i** were prepared from the corresponding 4-chromanone (**85g** and **85h**) and thiochromanone **85i** in quantitative yields (entries 5-7).^{27,28,58,59} By applying the same general method dihydrobenzo[*b*]oxepine **87b** was obtained in 93% yield (entry 8).⁶⁰ Reduction of hydroxy ketone **85j** followed by dehydration with phosphoric acid (H₃PO₄) instead of TsOH.H₂O gave alkene product **88j** in 85% yield (entry 9).³⁷ The use of TsOH.H₂O resulted in low yield (58%) when compared to (H₃PO₄). The methoxy functionalized ketones **85k** and **85c** were also transformed into cyclic alkenes **1k** and **1c** in 93% and 76% yields, respectively (entries 10 and 11).^{27,61,62} The appropriate selection of protecting groups in organic synthesis is crucial for the successful construction of the molecular framework.⁶³ The acetyl, benzoyl, tosyl and Fmoc protected amino ketones (**85l-85p**) were smoothly converted into desired olefinic substrates (**1l-1p**) in good yields (entries 12-16).^{27,64} Reduction of 2-phenyl substituted chromanone **85q** and quinolinone **85r** with NaBH₄ resulted in corresponding intermediate alcohols in 75% and 97% crude yields, respectively. However their dehydration in the presence of TsOH.H₂O or H₃PO₄ gave unstable unidentified products (entries 17 and 18).

Table 5. Preparation of cyclic olefinic substrates via reduction/dehydration

Entry	Substrate	Conditions	Product	Yield% ^a
1		i) 0.75 equiv NaBH ₄ , THF EtOH, 0 °C to rt, 1.5 h ii) cat. TsOH.H ₂ O, toluene 130 °C, 1 h		87
2		i) 1.0 equiv NaBH ₄ MeOH, 0 °C to rt, 2 h ii) cat. TsOH.H ₂ O, toluene 130 °C, 1 h		91
3		i) 0.98 equiv. NaBH ₄ MeOH, 0 °C to rt, 2 h ii) cat. TsOH.H ₂ O, toluene 130 °C, 1 h		92
4		i) 0.75 equiv NaBH ₄ , THF EtOH, 0 °C to rt, 2.5 h ii) cat. TsOH.H ₂ O, toluene 130 °C, 4 h		92
5		i) 0.75 equiv NaBH ₄ , THF EtOH, 0 °C to rt, 1.5 h ii) cat. TsOH.H ₂ O, toluene 130 °C, 2 h		72
6		i) 0.75 equiv NaBH ₄ , THF EtOH, 0 °C to rt, 6 h ii) cat. TsOH.H ₂ O, toluene 130 °C, 2 h		77
7		i) 0.75 equiv NaBH ₄ , THF EtOH, 0 °C to rt, 2.5 h ii) cat. TsOH.H ₂ O, toluene 130 °C, 2 h		73
8		i) 0.75 equiv NaBH ₄ , THF EtOH, 0 °C to rt, 1.5 h ii) cat. TsOH.H ₂ O, toluene 130 °C, 1 h		93
9		i) 1.0 equiv NaBH ₄ MeOH, 0 °C to rt, 1 h ii) H ₃ PO ₄ , THF, 80 °C, 2 h		76

10		i) 1.0 equiv NaBH ₄ MeOH, 0 °C to rt, 1 h ii) cat. TsOH.H ₂ O, toluene 130 °C, 2 h		93
11		i) 1.0 equiv NaBH ₄ MeOH, 0 °C to rt, 1.5 h ii) cat. TsOH.H ₂ O, toluene 130 °C, 1 h		76
12		i) 1.1 equiv NaBH ₄ MeOH, 0 °C to rt, 1 h ii) cat. TsOH.H ₂ O, toluene 130 °C, 1.5 h		78
13		i) 1.2 equiv NaBH ₄ MeOH, 0 °C to rt, 1.5 h ii) cat. TsOH.H ₂ O, toluene, 130 °C, 2 h		78
14		i) 3 equiv NaBH ₄ MeOH, 0 °C to rt, 1.5 h ii) cat. TsOH.H ₂ O, toluene 130 °C, 3 h		73
15		i) 2 equiv NaBH ₄ MeOH, 0 °C to rt, 1 h ii) cat. TsOH.H ₂ O, toluene 130 °C, 1 h		80
16		i) 2 equiv NaBH ₄ MeOH, 0 °C to rt, 1.5 h ii) cat. TsOH.H ₂ O, toluene 130 °C, 1.5 h		87
17		i) 0.75 equiv NaBH ₄ , THF EtOH, 0 °C to rt, 1.5 h ii) cat. TsOH.H ₂ O, toluene 130 °C, 2 h or ii) H ₃ PO ₄ , THF, 80 °C, 2 h		-
18		i) 0.75 equiv NaBH ₄ , THF EtOH, 0 °C to rt, 1.5 h ii) cat. TsOH.H ₂ O, toluene 130 °C, 2 h or ii) H ₃ PO ₄ , THF, 80 °C, 2 h		-

a) isolated yield

All the olefinic substrates (**1a**, **1c**, **1f-1r**, **87a**, **87b** and **88j**) were characterized by observing the double bond hydrogens peaks in ^1H NMR spectrum ranging from 5.60 to 6.54 ppm (**Figure 4**). The absence of carbonyl carbon and existence of two extra carbons in the unsaturated region of ^{13}C NMR spectra also confirm the olefinic substrates.

Figure 4. Selected ^1H NMR chemical shift data of the olefinic hydrogens

3.1.2 Preparation of ketone precursors for reduction/dehydration

Most of the ketones of Table 5 are commercially available. The preparation of ketones which are not commercially available is described in following paragraphs. Ketone **85f** was synthesized using 1-naphthol (**89**) in 1,2-dichlorobenzene (**90**) in the presence of Lewis acid AlCl_3 in 70% yield (**Scheme 25**).⁴⁷

Scheme 25

The proposed mechanism is given below (**Scheme 26**). The ketone tautomer **91** of naphthol **89** reacts with AlCl_3 giving **92**. The attack of double bond of intermediate **92** on another AlCl_3 molecule results in intermediate **93**. Electrophilic attack of 1,2-dichlorobenzene (**90**) on benzylic carbocation of **93** gives intermediate **94**. After deprotonation of **94**, the aromaticity is restored forming **95**. Treatment with water gives the desired ketone **85f**.⁶⁵

Scheme 26

^1H NMR spectrum displays doublet of doublets of benzylic hydrogen at 4.28 ppm. The peak at 197.3 ppm in ^{13}C NMR spectrum is associated to the carbonyl carbon of ketone **85f** (Figure 5).

Figure 5. Characteristic ^1H and ^{13}C NMR signals of ketone **85f**

The preparation of chromene **1h** was first attempted by cyclization of an *o*-allylic phenol (**98**) with palladium(II) salt.⁶⁶ The *o*-allylic phenol (**98**) was prepared using phenol (**96**) and prenyl bromide (**97**) in the presence of Na in anhydrous ether in 80% yield.⁶⁷ When the *o*-allylic phenol (**98**) was subjected to the Pd mediated cyclization condition an inseparable mixture of 6- and 5-membered cyclic ethers **1h** and **99** was obtained in 59% yield in 2.6:1 ratio, respectively (Scheme 27).

Scheme 27

The proposed reaction mechanism for Pd mediated cyclization is given below (Scheme 28). The coordination of the $\text{Pd}^{(0)}$ catalyst to the double bond of allyl phenol **98** giving η^2 π -allyl complex **100**. An oxidative addition leads to a η^3 π -allyl complex **101**. Hydroxyl group being hard nucleophile, attacks the metal center forming complex **102**. This Pd complex **102** undergoes substitution at the remote end of the allylic system followed by reductive elimination

affording the major six-membered ring product **1h** (endo-cyclization).^{68,69} Similarly exo-cyclization results in five-membered cyclic product **99**.⁶⁶

Scheme 28. Mechanism for cyclization of *o*-allylic phenol **98** with palladium⁽⁰⁾

The ¹H NMR spectrum shows the two methyl groups as a single intense singlet peak at 1.77 ppm for compound **98**. The benzylic and olefinic hydrogens of **98** give doublet and multiplet signals at 3.35 ppm and at 5.28-5.36 ppm, respectively, confirming the coupling of prenyl group to phenol moiety. The olefinic hydrogens give two doublets signals at 6.31 and at 5.60 ppm in ¹H NMR spectrum of cyclic ether **1h**. The methyl and two olefinic hydrogens of compound **99** appear as singlet and doublet at 1.77 and at 5.00 ppm, respectively (**Figure 6**).

Figure 6. Characteristic signals of ^1H and ^{13}C NMR of compounds **98**, **1h** and **99**

As the desired chromene **1h** could not be separated from the 5-membered isomeric **99**, we revised our strategy to obtain **1h**. The idea was to prepare 4-chromanone (**85h**) and convert it into cyclic alkene **1h** by reduction and dehydration protocol (Table 5, entry 6). Following the reported protocol of cyclization of hydroxyl acetophenone **105** and acetone (**106**) in the presence of pyrrolidine (**107**) afforded ketone **85h** in excellent yield (**Scheme 29**).⁷⁰

Scheme 29

The mechanism for the preparation of 4-chromanone (**85h**) displayed in **Scheme 30** demonstrates the formation of iminium ion **108** in the first step.⁷¹ The hydroxyl group of phenyl ketone **105** attacks the electrophilic carbon of iminium ion **108** giving oxonium intermediate **109**. After proton transfer steps, ammonium intermediate **111** is formed. The exclusion of amine **107** assisted by oxygen lone pair leads to **112**. The electrophilic carbon of oxonium ion **112** is attacked intramolecularly by enol and subsequent deprotonation leads to the ketone **85h**.

Scheme 30. Mechanism for the synthesis of 4-chromanone **85h**

The characteristic ^1H and ^{13}C NMR data of ketone **85h** are shown in **Figure 7**. The methylene hydrogens alpha to carbonyl group and two methyl groups are recognized as singlets at 2.73 ppm and at 1.46 ppm, respectively. The carbonyl carbon appears at 192.6 in ^{13}C NMR spectrum.

Figure 7. Characteristic ^1H and ^{13}C NMR signals of ketone **85h**

Alkylation of phenol (**96**) with ethyl 4-bromobutyrate (**115**) followed by base catalyzed hydrolysis afforded butyric acid **116** in 85% yield. The acid **116** was converted into ketone **86b** by poly phosphoric acid (PPA)-promoted Friedel Crafts acylation (**Scheme 31**).⁶⁰

Scheme 31

The structure of ketone **86b** was assigned by ^1H and ^{13}C NMR spectral data. In ^1H NMR, methylene hydrogens next to carbonyl carbon resonate at 2.90 ppm as triplet signal. Similarly, methylene hydrogens next to oxygen atom also give triplet signal but at 4.24 ppm. In ^{13}C NMR spectrum the carbonyl carbon of cyclic ketone **86b** is observed at 200.6 ppm (**Figure 8**).

Figure 8. Characteristic ^1H and ^{13}C NMR data of ketone **86b**

Following a reported protocol, nitration of 1-tetralone (**85a**) was carried out with HNO_3 in H_2SO_4 affording 7 and 5-nitro tetralones (**117** and **118**) in 59% and 18% yields, respectively (**Scheme 32**).³⁷

Scheme 32

Structural characterization was performed by means of spectral NMR data (**Figure 9**). The three aromatic hydrogens of compound **117** appear at 8.86, 8.30 and at 7.46 ppm as three doublets of doublets in ^1H NMR. Similarly the splitting pattern of the three aromatic hydrogens of compound **118** shows two doublets of doublets at 8.35 and 8.09 ppm and triplet at 7.48 ppm in ^1H NMR spectrum.

Figure 9. Characteristic ^1H and ^{13}C NMR signals of nitro ketones **117** and **118**

The hydrogenation of 7-nitro tetralone (**117**) into aniline derivative was performed using Pd/C as catalyst at 6 atm. pressure of H_2 . The amino tetralone **119** was obtained in 81% yield. Double reduction product, amino alcohol **120** was isolated in 13% yield (**Scheme 33**).³⁷

Scheme 33

The characteristic peak of NH_2 of amino ketone **119** in ^1H NMR appears as broad singlet at 3.73 ppm. The NH_2 hydrogens of amino alcohol **120** also appear as broad singlet but at 3.07 ppm in ^1H NMR. The aromatic hydrogens of both ketone **119** and alcohol **120** show considerable upfield shift in ^1H NMR when compared to nitro ketone **117**. Furthermore, the carbonyl carbon of ketone **119** in ^{13}C NMR data gives signal at 198.8 ppm. The benzylic carbon next to hydroxyl group of compound **120** resonates at 68.2 ppm (**Figure 10**).³⁷

Figure 10. Characteristic ^1H and ^{13}C NMR data of compounds **119** and **120**

The reported three component Mannich reaction of benzaldehyde (**121**), aniline (**122a**) and 2-hydroxyacetophenone (**105**) in the presence of iodine as a catalyst afforded phenylchroman-4-one (**85q**) in 53% yield (**Scheme 34**).⁷²

Scheme 34

The mechanism for the iodine catalyzed synthesis of 2-phenylchroman-4-one (**85q**) is given below (Scheme 35). In the first step the reaction between benzaldehyde (**121**) and aniline (**122a**) gives an imine **123**. The enol tautomer of hydroxy acetophenone (**124**) attacks the electrophilic carbon of the imine **123** catalyzed by I_2 forming intermediate **126**. The hydroxyl group attacks intramolecularly in S_N2 fashion leading to product **85q** (route A). In second route, the elimination of *N*-iodo aniline with the help of iodide anion gives intermediate **127**. The Michael addition type cyclization which is possibly catalyzed by the *in situ* formed *N*-iodoaniline-HI complex **128** results in the formation of ketone **85a** (route B).⁷²

Scheme 35. Mechanism for iodine catalyzed synthesis of Ketone **85q**

The ^1H NMR of **85q** shows two doublets of doublets at 2.90 and at 3.11 ppm for the two hydrogens at α -carbon of carbonyl group. The carbonyl carbon and methine carbon next to oxygen appear at 192 ppm and at 79.6 ppm, respectively (**Figure 11**).

Figure 11. Characteristic ^1H and ^{13}C NMR signals of ketone **122**

The smooth one-pot condensation/cyclization of *o*-aminoacetophenone (**129**) and benzaldehyde (**121**) in the presence of L-proline as organocatalyst delivered quinolin-4(1*H*)-one **130**.⁷³ After the protection of amine **130** with acetyl group quinolin-4(1*H*)-one **85r** was isolated in 81% yield (**Scheme 36**).⁷⁴

Scheme 36

The mechanism for the formation of quinolin-4(1*H*)-one **130** is given below (**Scheme 37**). The reaction of amine **129** and aldehyde **121** gives imine **131** in the first step. The reaction of ketone-imine **131** with proline **132** results in the formation of enamine **133**. The intramolecular nucleophilic attack of β -carbon of the enamine **133** at electrophilic carbon of imine gives cyclized intermediate **135**. Hydrolysis of the intermediate **135** forms ketone **130**.⁷³

Scheme 37. Mechanism for L-proline catalyzed synthesis of ketone **130**

The ^1H NMR data of compound **130** indicates multiplet at 2.74–3.00 ppm for the two hydrogen atoms at α -carbon of carbonyl group and a broad singlet for NH hydrogen at 4.50 ppm. The carbonyl carbon appears at 193.2 ppm in ^{13}C NMR spectrum for the mentioned compound. The methyl hydrogens of acetyl group give sharp singlet at 2.44 ppm for compound **85r** in ^1H NMR data and amide carbon appears at 170.1 ppm in ^{13}C spectral data (**Figure 12**).

Figure 12. Characteristic ^1H and ^{13}C NMR signals of compounds **130** and **85r**

3.1.3 Preparation of trisubstituted olefinic substrates via Grignard protocol

The olefinic substrates containing trisubstituted double bond were prepared from the corresponding ketones employing Grignard reaction procedure followed by *in situ* dehydration with 10% HCl (Table 6). The Grignard reagent was prepared from methyl iodide reaction with metallic magnesium in the presence of catalytic amount of molecular iodine in anhydrous diethyl ether as solvent. The ketones were added to the reaction mixtures after the disappearance of all magnesium. The tertiary alcohols formed as intermediates were treated with 10% HCl to afford dehydrated alkenes. α -Tetralone (**85a**), under these conditions gave trisubstituted alkene **1aa** in 76% yield (entry 1).²⁷ Reaction employing chromanones **85g** and **85h** afforded desired products in 78% and 83% yields, respectively (entries 2 and 3). Seven-membered ring alkenes **87aa** and **87bb** were also isolated in good yield under similar reaction conditions (entries 4 and 5).²⁷

Table 6. Preparation of trisubstituted alkenes via Grignard reaction

Entry	Substrate	Product	Yield% ^{a,b}
1	85a	1aa	76
2	85g	1gg	78
3	85h	1hh	83
4	86a	87aa	77
5	86b	87bb	87

a) isolated yield. b) i) 3.4 equiv Mg/MeI, Et₂O, 3 h; ii) 10% HCl, 12 h.

The ^1H and ^{13}C NMR spectral data of the trisubstituted alkenes listed in Table 6 are identical with those reported in literature (**Figure 13**).^{27,75-78} Representative signals in ^1H NMR are the methyl groups and olefinic hydrogens attached to the trisubstituted double bond. The signals of both methyl group and olefinic hydrogen appear as multiplets at 2.03-2.06 and at 5.82-5.87 ppm, respectively for compound **1aa**. Methyl groups of chromenes **1gg** and **1hh** give quartet and doublet signals at 1.98 ppm. Signals at 5.59-5.54 ppm as multiplet and 5.38 ppm as doublet are assigned to the hydrogen of double bond in compound **1gg** and **1hh**. The methyls of seven-membered alkene **87aa** and **87bb** show doublet signals at 2.09 and 2.14 ppm, respectively. The disappearance of carbonyl carbon and the presence of two olefinic carbons in ^{13}C NMR also helped in structures confirmation. The carbons belong to methyl groups give signals in saturated region of ^{13}C NMR at 19.3, 17.8 and 17.9 ppm for alkene **1aa**, **1gg** and **1hh**, respectively. In the case of seven-membered olefins **87aa** and **87bb**, the methyl group carbons observe slightly downfield at 22.6 and 24.6 ppm respectively.

Figure 13. Characteristics ^1H and ^{13}C NMR data of trisubstituted alkenes

3.1.4 Preparation of protected amine tetralones

The protected amine tetralones **85l**-**85p** (used to synthesize protected olefinic substrates, Table 5, section 3.1.1) were prepared as reported in literature (Table 7). The acetylation of tetralone **136** and **137** was achieved using DMAP, Ac₂O in Et₃N as solvent giving desired acetyl protected ketones **85l** and **85p** in 86% and 97% yields, respectively (entries 1 and 2).^{27,37} Amine tetralone **136** in the presence of BzCl, Et₃N and DCM as solvent gave benzoyl protected amine **85m** in 89% yield (entry 3).⁷⁹ The tosyl protected amine tetralone **85n** was obtained in 96% yield in pyridine with *p*-TsCl (entry 4).⁸⁰ In a similar manner, base labile Fmoc protected amine **85o** was formed in 98% yield with Fmoc-Cl and pyridine in DCM (entry 5).⁸¹

Table 7. Synthesis of protected amines

Entry	Substrate	Conditions	Product	Yield% ^a
1		3.4 equiv Ac ₂ O, 2.6 mol% DMAP, Et ₃ N, rt, 1 h		86
2		3.4 equiv Ac ₂ O, 2.6 mol% DMAP, Et ₃ N, rt, 1 h		97
3		1.4 equiv BzCl, 1.1 equiv Et ₃ N, DCM, rt, 3 h		89
4		1.35 equiv PTsCl, Pyridine reflux, 16 h		96
5		1.1 equiv Fmoc-Cl, 1.2 equiv pyridine, DCM 0 °C to rt, 1 h		98

a) isolated yield

Methyls of the acetyl groups appear as intense singlets at 2.21 and at 2.22 ppm in ^1H NMR spectra of compounds **85i** and **85p**, respectively. Peaks at 24.7 and at 23.3 ppm in ^{13}C NMR spectrum are assigned to the methyls of **85i** and **85p**, respectively. The carbonyl carbon of amide appears in ^{13}C NMR analysis at 168.8 and at 169.1 ppm, respectively.^{27,37} The presence of benzoyl group is confirmed by five additional aromatic hydrogens in ^1H NMR spectrum of compound **85m**. Furthermore, six extra aromatic carbons along with $-\text{CONH}$ peak at 165.8 ppm are observed in ^{13}C NMR spectrum of protected amine **85m**.⁸² The methyl of tosyl group of **85n** appears as sharp singlet at 2.39 ppm in ^1H NMR data.⁸³ The benzylic hydrogen of Fmoc-group and OCH_2 are shown as a triplet at 4.27 ppm and doublet at 4.57 ppm in ^1H NMR spectrum, respectively. The carbonyl carbon corresponds to OCONH in Fmoc group of **85o** giving signal at 152.9 ppm in ^{13}C NMR data (**Figure 14**).

Figure 14. Characteristics ^1H and ^{13}C NMR data of protected amines

3.1.5 Preparation of phenolic substrates via demethylation of methyl ethers

Methyl ether **1k** was demethylated using sodium ethanethiolate (generated *in situ*) in DMF at 140 °C giving phenol **88k** in 97% yield (Table 8, entry 1).^{84,85} In similar way, 6-methoxy-1,2-dihydronaphthalene (**1c**) was also demethylated into corresponding phenolic alkene **88c** in 80% yield (entry 2).

Table 8. Deprotection of methoxy substituted 1,2-dihydronaphthalenes into phenol derivatives

Entry	Substrate	Product	Yield% ^{a,b}
2	1k	88k	97
3	1c	88c	80

a) Isolated yield. b) 43.3 equiv NaH, 30 equiv EtSH, DMF, 0 °C-reflux, 5 h

The absence of intense singlet peak at 3.78 and at 55.1 ppm in ¹H and ¹³C NMR data, respectively is a strong evidence for the demethylated products **88k** and **88c**. Only two peaks in saturated region of ¹³C NMR data are detected for compounds **88k** and **88c** at 22.9, 27.8 ppm and 23.5, 26.6 ppm, respectively. The phenolic hydrogens appear at 4.85 and at 4.59 ppm as singlet for compounds **88k** and **88c**, respectively (**Figure 15**).⁸⁴

Figure 15. Characteristics ¹H and ¹³C NMR data of **88k** and **88c**

3.1.6 Preparation of acetyl and benzoyl protected olefinic substrates

The acetylation of phenols **88j**, **88k** and **88c** was accomplished with DMAP, Ac₂O in Et₃N as solvent,²⁷ leading to protected alkenes **138j**, **138k** and **138c** in 96%, 85% and 80% yields, respectively (Table 9, entries 1-3). The phenol **88j** was protected with benzoyl group in 94% yield using BzCl and Et₃N as a base (entry 4).⁷⁹

Table 9. Protection of phenolic alkenes with acetyl and benzoyl groups

Entry	Substrate	Condition	Product	Yield% ^a
1	88j	3.8 equiv Ac ₂ O, 2.8 mol% DMAP, Et ₃ N, rt, 1.5 h	138j	96
2	88k	3.8 equiv Ac ₂ O, 2.8 mol% DMAP, Et ₃ N, rt, 2 h	138k	85
3	88c	3.8 equiv Ac ₂ O, 2.8 mol% DMAP, Et ₃ N, rt, 1.5 h	138c	80
4	88j	1.1 equiv BzCl, 2.2 equiv Et ₃ N, DCM, rt, 3 h	138s	94

a) Isolated yield

The methyl hydrogens of acetyl groups are observed at 2.21, 2.27 and 2.28 ppm, respectively as intense singlet peaks in ¹H NMR spectra. The carbonyl carbons of the acetyl groups give signals at 169.1, 169.6 and 169.7 ppm, respectively, in ¹³C NMR.^{86,87}

The presence of five additional aromatic hydrogens in ¹H NMR data confirms the coupling product **138s**. In addition, ¹³C NMR spectrum shows the presence of carbonyl carbon at 164.8 ppm for compound **138s** (Figure 16).

Figure 16. Characteristics ^1H and ^{13}C NMR data of **138j**, **138k**, **138c** and **138s**

3.1.7 Preparation benzo-methylene **139** via Wittig reaction

Wittig reaction was used to prepare benzo-methylene **139** from ketone **85a**. The triphenyl phosphonium ylide was generated *in situ* from $\text{MeP(Ph)}_3\text{Br}$ and *t*-BuOK as base in anhydrous Et_2O . The exocyclic alkene **139** was obtained in 97% yield (**Scheme 38**).⁸⁸

Scheme 38

The Wittig reaction mechanism is given below (**Scheme 39**).⁸⁹ In the initial step direct irreversible [2+2] cycloaddition addition of ylide **141** and ketone **85a** gives an oxaphosphetane **142** as an intermediate. The irreversible decomposition of oxaphosphetane **142** forms alkene **139** and phosphine oxide (**143**). The driving force of the Wittig reaction is the formation of highly stable double bond between phosphorus and oxygen in phosphine oxide.

Scheme 39. Wittig reaction mechanism

The formation of olefin **139** is confirmed by ^1H and ^{13}C NMR (**Figure 17**). The two hydrogens of the exocyclic double bond give signals at 4.94 and at 5.50 ppm both as doublet. In ^{13}C spectra, the methylene carbon of exocyclic double bond appear at 107.8 ppm and quaternary carbon at 143.4 ppm.⁸⁸

Figure 17. Characteristics ¹H and ¹³C NMR data of compound **139**

3.1.8 Summary of the prepared cyclic olefins

In summary, several cyclic olefinic substrates were synthesized, including 1,2-dihydronaphthalenes substituted with aryl and methyl at position 1 or at aromatic ring with nitrogen and oxygen (protected with acetyl, benzoyl and Fmoc). Chromenes, thiochromenes, and seven-membered ring substrates were also prepared (**Figure 18**).

Figure 18. Cyclic olefins prepared for reaction with I(III)

3.1.9 Synthesis of chiral iodoarene compounds

To explore enantioselective ring contraction reaction with hypervalent iodine(III) compounds, several optically active chiral aryl iodide reagents (**36a**, **36i** and **36m-36r**) were synthesized (**Figure 19**).

Figure 19. Chiral aryl iodide reagents

The Mitsunobu reaction of 2-iodophenol (**144**) with chiral non-racemic (–)-lactic acid ethyl ester (**35**) in the presence of DIAD and PPh₃ gave chiral iodoarene **36m** in 92% yield with inversion of configuration (**Scheme 40**).⁴⁹

Scheme 40

The mechanism of the Mitsunobu reaction is given below (**Scheme 41**). Triphenyl phosphine (**145**) makes a nucleophilic attack on diisopropyl azodicarboxylate (**146**) producing a betaine **147**, which deprotonates the iodo phenol (**144**) forming the iodophenoxide **148** and phosphonium moiety **149**. The attack of alcohol **35** on phosphonium **149** gives another phosphoxonium **150** with elimination of diamine moiety. The phenoxide ion **148** attacks on **150** pushing out triphenyl phosphonium oxide **143** resulting in formation of **36m** with inversion of configuration.⁹⁰

Scheme 41. Mechanism for Mitsunobu reaction

The iodoarene **36m** was hydrolyzed into corresponding chiral iodoarene acid **36s** in 98% yield using 2M NaOH solution in MeOH/THF as solvent (**Scheme 42**).⁴⁹

Scheme 42

The two methyl groups of compound **36m** appear at 1.24 and at 1.70 ppm as triplet and doublet, respectively in ¹H NMR spectrum. Four aromatic hydrogens at 7.78 ppm, 7.25 ppm

and 6.73 ppm (2H) are identified for compound **36m**. The presence of six aromatic carbons together with two methyl carbons at 14.1 and at 18.5 ppm in ^{13}C NMR verify coupling product **36m**.⁴⁹ The absence of OCH_2CH_3 peaks in ^1H and ^{13}C NMR data confirm the hydrolyzed product **36s** (**Figure 20**).⁴⁹

Figure 20. Characteristics ^1H and ^{13}C NMR data of **36m** and **36s**

A number of single arm chiral iodides were synthesized via Steglich esterification and amidation protocol (Table 10).⁹¹ Reaction of acid **36s** with (–)-menthol (**26**) in the presence of DCC as a coupling reagent and DMAP as a catalyst gave ester **36p** in 94% yield (entry 1).⁹² The coupling of commercially available 2-iodobenzoic acid (**36t**) with (–)-menthol (**26**) under the same reaction conditions resulted in iodo arene **36o** in 96% yield (entry 2).⁹³ Amide derived chiral iodoarenes **36q** and **36r** were synthesized in 80% and 82% yields, respectively, from aryl iodo acid **36s** and the corresponding anilines **122a** and **122b** (entries 3 and 4).

Table 10. Synthesis of chiral iodoarenes via Steglich protocol

Entry	Substrate	Product	Yield% ^{a,b}
1			94
2			96
3			80
4			82

a) Isolated yield. b) 1.25 equiv DCC, 15 mol% DMAP, DCM, 6 h

The mechanism for Steglich esterification is given below (**Scheme 43**). In the first step, the lone pair of electrons on nitrogen atom of the DCC (**152**) takes acidic hydrogen from **151**. The attack of carboxylate anion **153** on the protonated carbodiimide **154** produces *O*-acylisourea **155**. Proton transfer step followed by attack of DMAP (**157**), a stronger nucleophile than alcohol, on carbonyl carbon of *O*-acylisourea **156** gives reactive amide **158**. The alcohol attacks at the electrophilic carbon of amide **159** affording ester **160**.⁹¹

Scheme 43. Mechanism for Steglich Esterification

The ^1H NMR peaks at 0.52 and at 0.73 ppm represent isopropyl group in compound **36p**. ^1H NMR signals at 0.90 and at 1.70 ppm are assigned to the two methyl groups of aryl iodide moiety **36p**. In addition, the presence of carbonyl and carbinolic carbon at 171.4 and at 75.5 ppm, respectively, helped in elucidation of structure **36p**.⁹²

The carbinolic hydrogen of aryl iodide **36o** in ^1H NMR data resonates at 4.96 ppm as a triplet of doublets. Furthermore, the carbonyl and carbinolic carbon of compound **36o** in ^{13}C NMR spectrum are observed at 166.2 and 75.9 ppm respectively.⁹³

The ^1H NMR spectrum of compound **36q** indicates signal of amide -NH as broad singlet at 8.02 ppm. The methyl group of lactate moiety appears at 1.73 as a doublet. ^{13}C NMR spectrum shows quaternary carbon signal at 169.1 ppm for CONH of compound **36q**.

The two methyl groups of aniline moiety in compound **36r** are observed at 2.19 ppm as singlets, whereas, NH hydrogen is found as broad singlet at 8.07 ppm in ^1H NMR spectrum. ^{13}C NMR confirms the presence of two methyl carbon at 18.4 ppm and carbonyl carbon at 169.6 ppm for compound **36r** (Figure 21).

Figure 21. Characteristics ^1H and ^{13}C NMR data of single arm chiral aryl iodides

The “two arms” lactate based chiral aryl iodide **36a**, which has proven to be an effective reagent for asymmetric transformations, was prepared using reported protocol.⁴⁹ The first step is the treatment of resorcinol (**161**) with iodine in the presence of NaHCO₃ giving iodide **34**, in 71% yield (**Scheme 44**).^{94,95}

Scheme 44

The ¹H NMR shows a doublet at 6.46 ppm for two equivalent hydrogen atoms and a triplet for single hydrogen at 7.00 ppm. Similarly, the presence of ¹³C NMR peak at 77.6 ppm confirms the aromatic carbon bonded to iodide (**Figure 22**).⁹⁵

Figure 22. Characteristics ¹H and ¹³C NMR data of **34**

The Mitsunobu reaction of 2-iodoresorcinol (**34**) with (–)-lactic acid ethyl ester (**35**) in the presence of DIAD and PPh₃ gave chiral iodoarene (**36a**) in 94% yield with inversion of stereochemistry (**Scheme 45**).⁴⁹

Scheme 45

The other enantiomer (2*S*,2*S*)-**36a** was prepared in 84% yield using the same Mitsunobu protocol (**Scheme 46**).

Scheme 46

Further modification of two arms aryl iodide **36a** is demonstrated below (Scheme 47). The chiral aryl iodide **36a** was hydrolyzed in a similar fashion as described for aryl iodo acid **36s** to corresponding carboxylic acid **36b** without epimerization.⁴⁹ The C₂-symmetric mesitylamine derived aryl iodide **36i** was also prepared according to known protocol.^{49,52} The treatment of acid **36b** with thionyl chloride followed by mesitylamine gave amide **36i** in good yield.

Scheme 47

Chiral iodoarenes (**36a**, **36b** and **36i**) are characterized by ¹H and ¹³C NMR spectral data (Figure 23). The triplet signal at 1.24 ppm is assigned to methyl of OCH₂CH₃ group of compound **36a**. The methyl group at chiral center appears as doublet signal at 1.69 ppm. The quartet signal at 4.75 ppm represents hydrogen of the chiral center of **36a**. ¹³C NMR demonstrates the presence of carbonyl carbon of ester functionality at 171.6 ppm for compound **36a**.⁴⁹

The absence of OCH₂CH₃ peaks in ¹H and ¹³C NMR spectra confirm the successful formation of acid **36b**.⁴⁹

The ¹H NMR shows two singlets at 2.15 (for 12H, 4 equivalent CH₃) and 2.27 (for 6H, 2 equivalents CH₃) ppm for the methyl groups of MsNH₂ confirm the formation of desired

coupling product **36i**. A broad singlet is observed at 8.00 ppm for two NH hydrogens. The ^{13}C NMR shows carbonyl carbon at 169.6 ppm and methyl carbons of trimethyl aniline at 18.8 and 20.9 ppm.⁴⁹

Figure 23. Characteristics ^1H and ^{13}C NMR data of two arms chiral aryl iodides

3.2 Ring contraction reactions mediated by HTIB

3.2.1 Oxidation of 2*H*-chromenes and 2,3-dihydrobenzo[*b*]oxepines with iodine(III)

Our group has developed the HTIB mediated ring contraction of 1,2-dihydronaphthalenes into indanes.^{27,28} The mentioned rearrangement was applied in the diastereoselective total synthesis of (+)-mutisianthol⁴⁶ and (±)-indatraline.²⁸ This encouraged us to examine the behavior of 2*H*-chromenes and their derivatives with I(III), aiming to obtain functionalized 2,3-dihydrobenzofurans (**Figure 24**).

Figure 24. I(III)-mediated ring contraction in 2*H*-chromenes

Many biologically active 2,3-dihydrobenzofurans were isolated from natural sources. A few illustrative examples are shown in **Figure 25** for natural products with *trans*-relative configuration and in **Figure 26** for natural products with *cis*-relative configuration.

Figure 25. 2,3-Dihydrobenzofurans skeleton with *trans*-relative configuration

Figure 26. 2,3-Dihydrobenzofurans skeleton with *cis*-relative configuration

We focused our initial efforts on 2*H*-chromene **1g**, which was easily prepared in high yield from the commercially available 4-chromanone (**85a**) (Table 5, entry 5). Based on our previous experience,^{27,28,96} HTIB was selected among several available hypervalent iodine(III) reagents. The reactions of **1g** were carried out with varying solvents (MeOH, TMOF, TEOF, CH₃CN, TFE, HFIP and DCM) and temperatures. The results obtained are summarized in Table 11. The reaction in MeOH and TMOF gave methoxy substituted 4*H*-chromene **174g**, as the main product, together with the *trans*-addition product **175g** (entries 1 and 2). Using MeOH and BF₃.OEt₂ chromene **174g** was obtained in lower yield when compared to reaction in pure methanol. However, **175g** was isolated in higher yield (entry 3). The reaction conducted in TEOF gave **176g** in 42% yield (entry 4). The reaction carried out in TFE and in TFE/BF₃.OEt₂ led to trifluoroethoxy substituted 4*H*-chromene **178g** in 24% and 23% yields, respectively. Conversely, the addition product was not isolated (entries 5 and 6). Screening with some other solvents, such as CH₃CN, HFIP and DCM resulted in complex mixtures (entries 7-11). Unfortunately, the desired ring contraction product was not obtained in any of the reactions performed.

Table 11. Oxidation of 2*H*-chromene (**1g**) with 1.1 equiv HTIB

Entry	Conditions	Product (Yield%) ^a
1	MeOH, 0 °C, 3 h
2	TMOF, 0 °C, 2 h
3	MeOH, BF ₃ .OEt ₂ , 0 °C, 2.5 h
4	TEOF, 0 °C to rt, 4 h
5	TFE, 0 °C, 2 h
6	TFE, BF ₃ .OEt ₂ , 0 °C, 30 min
7	CH ₃ CN, 0 °C	complex mixture
	1. HFIP/DCM (1:4)	
8	H ₂ O (22 equiv) 0 °C	complex mixture
	2. NaBH ₄	
9	HFIP, 0 °C	unstable product
10	HFIP, BF ₃ .Et ₂ O, 0 °C	complex mixutre
11	DCM, 0 °C	complex mixture

a) Isolated yield

The results show the effect of oxygen atom on the course of the reaction by making carbinolic hydrogen acidic. The formation of **174g** can be explained by the mechanism described below (**Scheme 48**).^{23,27,30,97} The first step is an electrophilic attack of iodine(III) on the double bond forming the organoiodine **179**. The formation of free benzylic carbocation is also supported by computational calculation (unpublished). This intermediate is then attacked by the nucleophilic solvent at the benzylic carbon to form **180**. The final step is the β -elimination, displacing PhI and water to give substituted 4*H*-chromene **174g**.

Scheme 48. Mechanism for the formation substituted 4*H*-chromene

The proposed mechanism for *trans*-addition products is outlined below (**Scheme 49**). The nucleophilic attack of methanol at benzylic position of organoiodine intermediate **179** results in the formation of adduct **181**. The lone pair of methoxy group in **180** attacks intramolecularly at the carbon atom kicking out PhI giving oxonium **182**. The attack of another methanol molecule at benzylic position gives *trans*-product **175g**.^{27,28}

Scheme 49. Mechanism for the formation of *trans*-addition product

Considering that the less electronegative sulfur atom could have less pronounced effect on the course of reaction in comparison to oxygen atom, the behavior of *2H*-thiochromene **1i** was investigated (Table 12). The reaction of **1i** with HTIB in MeOH and in TMOF led to *4H*-thiochromene **183i**, similarly to chromene **174g** although in lower yield (entries 1 and 2). A two-fold increase in yield for substituted *4H*-chromene **184i** was observed using TEOF as solvent (entry 3). Fluorinated solvents like TFE and HFIP afforded no ring contraction or β -elimination products (entries 4 and 5).

Table 12. Oxidation of *2H*-thiochromene (**1i**) with 1.1 equiv HTIB

Entry	Condition	Product (Yield%) ^a
1	MeOH, 0 °C, 40 min	183i (29%)
2	TMOF, 0 °C, 30 min	183i (38%)
3	TEOF, 0 °C, 30 min	184i (60%)
4	TFE, 0 °C	complex mixture
5	1. HFIP/DCM (1:4) H ₂ O (22 equiv) 0 °C, 2. NaBH ₄	SM

a) Isolated yield

Taking into account that alkyl-substituted alkenes have different behavior when compared to nonsubstituted ones (see introduction; Table 1 and Table 2),^{28,36} the reaction of chromene **1gg** was also performed under several conditions (Table 13). Treatment of **1gg** with

HTIB in MeOH or in TMOF gave *cis*-dimethoxychromane **185gg** in a diastereoselective fashion and in good yield (entries 1 and 2). In this case neither substituted 4*H*-chromene nor *trans*-addition products were isolated. The relative configuration was assigned by NMR including NOESY experiments. Analogously, the reaction of **1gg** in TEOF gave **186gg** (entry 3). The fluorinated solvent TFE was also tested without success (entry 4).

Table 13. Oxidation of 4-methyl-2*H*-chromene (**1gg**) with 1.1 equiv HTIB

Entry	Condition	Product (Yield%) ^a
1	MeOH, 0 °C, 1 h	185gg (64%)
2	TMOF, 0 °C, 2 h	185gg (44%)
3	TEOF, 0 °C to rt, 2 h	186gg (58%)
4	TFE, 0 °C	complex mixture

a) Isolated yield

The formation of organoiodine **187** in the first step followed by attack of methanol at benzylic position gives intermediate **188**. The intermolecular displacement of PhI by MeOH in **189** leads to *cis*-addition product **185gg** (Scheme 50).²⁷

Scheme 50. Mechanism for the formation of *cis*-addition product

The assignment of structures was accomplished by the ^1H and ^{13}C NMR, LRMS, HRMS and IR spectroscopy. The significant ^1H and ^{13}C NMR signal are given below (**Figure 27**). The doublet signals between 5.20-5.81 ppm in ^1H NMR spectra indicate the benzylic hydrogen for substituted 4*H*-chromenes (**174g**, **176g** and **178g**) and thiochromenes (**183i** and **184i**). There are two well-resolved signals as doublet of doublets and doublet in the region 6.71-6.85 ppm and 5.85-6.14 ppm corresponding to olefinic hydrogens. Carbons signals from 75.0 to 95.8 ppm range are assigned to substituted benzylic carbon atoms in substituted chromenes and thiochromenes. Eight carbons signals in ^{13}C NMR in unsaturated region clearly indicate aromatic as well as olefinic functionalities. The signals for benzylic hydrogens of *trans*-addition product are found as doublet of doublets at 4.19 ppm and at 4.23-4.29 ppm as multiplet (overlapped with OCH_2) for compounds **175g** and **177g**, respectively. The benzylic carbon resonates at 73.9 and at 73.2 ppm, respectively for the above mentioned *trans*-compounds. The chemical shift values for benzylic carbons of *cis*-addition products **185gg** and **186gg** appear at 74.4 and at 75.5 ppm, respectively.

Figure 27. Characteristics ¹H and ¹³C NMR data of chromanes

Data from the NOESY correlation experiments are used to elucidate the relative configuration of addition products. The important co-facial cross-peaks in NOESY spectra arise from spatial interaction are shown below (**Figure 28**). Through space correlations between Ha and Hb, Hb and OMe², Ha and OMe² indicate that these hydrogens and methoxy are on the same side in compound **175g**. Similarly, the sequential correlations between Ha, Me, Me, Hb and Hc help us in assigning the relative stereochemistry of compound **185gg**. The spatial

interaction between Ha and Me, Me and Hb supported *cis*-relative configuration of compound **186gg**.

Figure 28. Key NOESY interactions of **175g**, **185gg** and **186gg**

In the seven membered ring substrates **87b** and **87bb** the possibility of β -elimination (**Scheme 48**) could be avoided due to the presence of an additional methylene carbon. When the alkene **87b** was treated with HTIB in TFE, to our delight the ring contraction product **190b** was obtained in good yield (Table 14, entry 1). Using the mixed solvent system HFIP/DCM followed by *in situ* reduction with NaBH_4 led to the hydroxy functionalized chromane **191b** in excellent yield (entry 2). Carrying out the same reaction but without the addition of H_2O afforded tosylated acetal product **192b** in 34% yield together with aldehyde **193b** in 15% yield (entry 3). Aldehyde **193b** was difficult to purify due to minor impurities that coeluted with the desired product and instability. The addition of small amount of water is necessary to decrease the formation of undesired tosylated acetal product **192b**. Furthermore, using MeOH as the solvent allowed us to isolate the expected ring contraction acetal product **194b** in good yield (entry 4). The methyl oxepine **87bb** also experienced ring contraction providing the keto substituted chromane **195bb** in good yield (entry 5).

Table 14. Oxidation of 2,3-dihydrobenzo[*b*]oxepine **87b** and **87bb** with HTIB

Entry	Substrate	Conditions	Product (Yield%) ^a
1		1.2 equiv HTIB, TFE 0 °C, 15 min	190b (55%)
2	87b	1. 1.1 equiv HTIB HFIP/DCM (1:4) 22 equiv. H ₂ O, 5 min 2. NaBH ₄ , 2 h	191b (87%) + 192b (9%)
3	87b	1.1 equiv HTIB HFIP/DCM (1:4), 5 min	192b (34%) + 193b (15%)
4	87b	1.5 equiv HTIB, MeOH/DCM (4:1), 0 °C, 5 h	194b (51%) + SM (20%)
5		1.1 equiv HTIB TFE, 0 °C, 30 min	195bb (58%)

a) Isolated yield

The mechanism for the ring contraction of **87b** in HFIP/DCM is depicted in **Scheme 51**. The electrophilic attack of HTIB on the double bond gives carbocation **196**. The oxygen lone pair attacks at benzylic carbon resulting in the cyclic oxonium ion **197**. Ring opening of the four-membered ring moiety of **197** gives iodonium intermediate **198**. The migration of an aryl bond leads **198** to intermediate **199**. After proton transfer, aldehyde **193b** is reduced to alcohol **191b**.^{24,27,28}

Scheme 51. Mechanism for the ring contraction of **87b** in HFIP/DCM

The acetal **190b**, **192b** and **194b** are recognized by the characteristic chemical shifts of acetal hydrogens and carbons in ^1H and in ^{13}C NMR spectra (**Figure 29**). The acetal hydrogen for compounds **190b**, **192b** and **194b** appear as doublets at 4.85, 6.59 and 4.45 ppm in ^1H NMR, respectively. Acetal carbons are observed at 105.8, 100.3 and 107.6 ppm, respectively. The hydroxy-methylene hydrogens of chromane **191b** give two doublets of doublets signals at 3.80 and at 3.89 ppm. Peak at 208.8 ppm indicates the carbonyl carbon of keto-chromane **195bb**.

Figure 29. Characteristics ^1H NMR and ^{13}C NMR data of chromanes

Several reaction conditions were tested for 2,2-dimethyl-2H-chromene **1h** (Table 15). In this case, we were expecting ring contraction product as there is no hydrogen atom at carbinolic carbon, which is responsible for the formation of 4H-chromene, such as **174g** (**Scheme 48**). Ring contraction product, such as the hydroxyl functionalized benzofurane **200h** was indeed

isolated using the mixed solvent system HFIP/DCM followed by *in situ* reduction with NaBH₄ although in low yield (entry 1). In MeOH and in TMOF ring contraction acetal product **201h** was obtained but in low yield (entries 2 and 3). Starting material was recovered when DIB was used in place of HTIB (entry 4). DIB and BF₃.OEt₂ led to the required product **201h** in low yield (entry 5). Intense efforts were made to improve these yields, but without success (entries 6-8).

Table 15. Oxidation of dimethyl-2*H*-chromene **1h** with 1.1 equiv of I(III)

<div style="display: flex; align-items: center; justify-content: space-between;"> <div style="text-align: center;"> <p>1h</p> </div> <div> <p>1.1 equiv HTIB or DIB</p> <p>→</p> </div> </div>		
Entry	Conditions	Product (Yield%) ^a
1	1. HTIB, HFIP/DCM (1:4) 22 equiv. H ₂ O, 5 min 2. NaBH ₄ , 2 h	<p>200h (31%)</p>
2	HTIB, MeOH, 0 °C, 2 h	<p>201h (30%)</p>
3	HTIB, TMOF, 0 °C, 3 h	<p>201h (17%)</p>
4	DIB, MeOH, 0 °C, 3 h	starting material recovered
5	DIB, MeOH, BF ₃ ·OEt ₂ , 0 °C, 2 h	<p>201h (12%)</p>
6	HTIB, TFE, 0 °C, 5 min	Complex mixture
7	HTIB, HFIP, 0 °C, 5 min	Complex mixture
8	HTIB, CH ₃ CN, 0 °C, 30 min	Complex mixture

a) Isolated yield

The behavior of methyl substituted chromene **1hh** was also investigated (Table 16). Analogous results were observed for 2,2,4-trimethyl-2*H*-chromene **1hh** (entries 1 and 2). All of

these efforts did not lead to improved yields. Application of TFE, CH₃CN and HFIP gave no expected products (entries 3-5).

Table 16. Oxidation of dimethyl-2*H*-chromene **1hh** with 1.1 equiv HTIB or DIB

Entry	Conditions	Product (Yield%) ^a
1	MeOH, 0 °C, 1 h	(24%)
2	MeOH/Et ₂ O, 0 °C, 1 h	(24%)
3	TFE, 0 °C, 5 min	Complex mixture
4	CH ₃ CN, 0 °C, 20 min	Complex mixture
5	HFIP/DCM (1:4), 0 °C, 5 min	Complex mixture

a) Isolated yield

The ring contractions in MeOH mediated by HTIB can be explained by the mechanism given below (**Scheme 52**). In first step, the electrophilic attack of iodine(III) on the double bond of alkene **1h** results in the formation of organoiodine **203**. The attack of nucleophilic solvent (MeOH) on benzylic carbocation gives adduct **204**. The anti-periplanarity required for the rearrangement is accomplished by equilibration of adduct **204** to its more stable conformational isomer **205**. After protonation and migration of an aryl bond pushing out PhI and H₂O gives the ring contraction intermediate **207**. The oxonium **207** is attacked by nucleophilic solvent forming acetal **201h**.^{27,28}

Scheme 52. Mechanism for the ring contraction of **1h** in MeOH

The structures of benzofurans **200h**, **201h** and **202hh** were assigned by ^1H and ^{13}C NMR data. Methylene hydrogens next to hydroxyl group of compound **200h** are observed as doublet at 3.87 ppm. A clear triplet signal is found for benzylic hydrogen at 3.21 ppm. Quaternary carbinolic carbon attached to methyl groups appear at 88.4, 88.3 and 88.4 ppm, respectively for compound **200h**, **201h** and **202hh** in ^{13}C . The acetal carbon of compound **201h** gives signal in downfield region at 103.9 ppm. The ^{13}C spectrum for benzofuran **202hh** shows carbonyl carbon at 207.4 ppm (**Figure 30**).

Figure 30. Characteristics ^1H NMR and ^{13}C NMR data of **200h**, **201h** and **202hh**

3.2.2 Synthesis of functionalized indanes with HTIB

Indane skeleton occurs in many biologically active natural products and pharmaceuticals, constituting an important target in organic synthesis and in drug discovery.⁹⁸⁻¹⁰³ Numerous synthetic methodologies have been developed to construct indane core including cyclization,¹⁰⁴⁻¹⁰⁶ cycloaddition¹⁰⁷⁻¹⁰⁹ and rearrangements.^{27,110-112} Indanes substituted in the aromatic ring by nitrogen¹¹³⁻¹¹⁷ or by oxygen¹¹⁸⁻¹²² are present in compounds with promising biological activities. The development of HTIB-mediated ring contraction of 1,2-dihydronaphthalenes into functionalized indanes^{27,28} motivated us to explore further the scope of this reaction focusing on ring contractions in oxygen and nitrogen substrates to broaden functional group compatibility and applications in total synthesis. Previously ring contraction with HTIB in substrates bearing methoxy group at the aromatic ring resulted in low yields (3-12%) of indanes (see Table 1, introduction).²⁷

Oxidation with HTIB was studied in protected 7-amine alkenes **1l-1o** (Table 17). The presence of electron donating group, such as amide *para* (position 7) to migrating carbon (position 4) at aromatic ring enhance the stability by mesomeric effect of benzylic carbocation formed which in turn increase the capability of oxidative rearrangement (see introduction; **Scheme 3**).^{27,37} The *N*-acetyl protected alkene **1l** was treated with HTIB in MeOH affording the desired indane **7l** in 67% yield (entry 1).²⁷ Benzoyl protected alkene **1m** also experienced ring contraction giving acetal product **7o** in 77% yield in MeOH/DCM (8:1) as solvent (entry 2). DCM was added to solubilize substrate **1m** and to increase the rate of reaction. When the reaction was tried in pure MeOH, indane **7m** was obtained in 51% yield and took 1 h to consume starting material (entry 3). The protecting group tolerance was further investigated with Fmoc protected alkene **1o** and the anticipated ring contraction product **7o** was isolated in 64% yield (entry 4).

Table 17. Reactions of Protected 7-amine alkenes **1l-1o** with HTIB at 0 °C

Entry	Substrate	Conditions	Product (Yield%) ^a
1		1.1 equiv HTIB, MeOH 10 min	(67%)
2		1.2 equiv HTIB MeOH/DCM (8:1) 10 min	(77%)
3		1.2 equiv HTIB, MeOH 1 h	(51%)
4		1.2 equiv HTIB MeOH/DCM (4:1) 10 min	(64%)

a) Isolated Yield

The reaction of tosyl protected 7-amine alkene **1n** with HTIB was also investigated under different reaction conditions (Table 18). Tosyl amide *para* to migrating carbon could also have facilitating effect on ring contraction by increasing electronic density. However, only the formation of addition products *trans*-**8n** and *cis*-**8n** were observed in MeOH and in DCM/MeOH as solvents (entries 1 and 2). Fluorinated solvents like TFE and HFIP proved to be ineffective under the reaction conditions (entries 3 and 4).

Table 18. Reaction of Tosylamide **1n** with HTIB

Entry	Conditions	Yield% ^a <i>trans</i> - 8n , <i>cis</i> - 8n , 1n
1	MeOH, 30 min	10, 37, 14
2	DCM/ 50 equiv MeOH 30 min	<i>cis</i> , <i>trans</i> addition products ^b
3	TFE, 10 min	complex mixture
4	H ₂ O, HFIP/DCM (1:4), 10 min	complex mixture

a) Isolated yield. b) GC monitored

The acetal **7l** is identified by the characteristic coupling constant of 7.5 Hz at 4.27 ppm in ^1H NMR. This hydrogen corresponds to the acetal hydrogen. Two methoxy groups of acetal resonate at 3.39 and at 3.37 ppm. The acetal carbon is observed at 107.2 ppm in ^{13}C NMR spectrum.²⁷ The typical coupling constant and chemical shift of acetal hydrogen and carbon respectively makes the ring contraction product distinguishable from *cis* and *trans*-addition products. Peaks appear as doublets at 4.29 and at 4.26 are assigned to acetals **7m** and **7o**, respectively. The distinctive acetal carbon in ^{13}C NMR appears at 107.1 ppm for both (**Figure 31**).^{27,28}

Figure 31. Characteristic ^1H NMR and ^{13}C NMR values of acetal **7l**, **7m** and **7o**

The relative configuration of the addition products is assigned based on the coupling constant of benzylic hydrogen with the neighboring hydrogen. The coupling constant for *trans*-**8n** and *cis*-**8n** are 4.8 and 2.7 Hz at 4.14 and at 4.26 ppm, respectively (**Figure 32**).²⁷

Figure 32. Characteristic ^1H NMR and ^{13}C NMR values of *trans*-**8n** and *cis*-**8n**

Next, oxidation in acetyl protected 6-amine alkene **1p** was explored. In this case, amide substituent *meta* to migrating carbon decreases the electronic density by inductive effect of nitrogen atom and does not increase directly the electronic density at migrating carbon by

mesomeric effect (see introduction; **Scheme 3**). Several conditions were tested for ring contraction of alkene **1p** (Table 19). Slow reaction and complex mixtures were observed for substrate **1p** using HTIB either in MeOH or in DCM/MeOH at different temperatures (entries 1-3). Fluorinated solvents, such as TFE and HFIP/DCM, also did not provide ring contraction product (entries 4 and 5). In contrast to 7-acetamide **11**, the electronic effect explained above might be the probable reason for not getting desired product.

Table 19. Reaction of 6-acetamide **1p** with HTIB

Entry	Solvent	Temp.	Result ^a
1	MeOH	0 °C to rt	complex mixture
2	DCM/50 equiv MeOH	0 °C to rt	complex mixture
3	MeOH	40 °C	complex mixture
4	TFE	0 °C	complex mixture
5	H ₂ O, HFIP/DCM (1:4)	0 °C	complex mixture

a) By TLC and GC

Previously our group has investigated the oxidation of substrates bearing methoxy group at the aromatic ring with HTIB. The desired indanes were isolated in low yields (3-12%) together with addition products.²⁷ Iodine(III) is known to act as single-electron-transfer (SET) for methoxy substituted aromatic compounds forming reactive cation radical intermediates.^{123,124} The generation of these cation radicals could be a possible reason of reaction failure due to their high susceptibility towards nucleophilic attack and other side reactions. We consider that the ring contraction could take place with an acetyl group instead of a methoxy making ring contraction useful in the synthesis of oxygen functionalized indanes. It should be noted that electron donating groups in substrate facilitated the ring contraction product (Table 17), while electron withdrawing substituent by inductive effect hampered the formation of desired indane (Table 19). Several reaction conditions were tested for ring contraction reaction in oxygenated substrate **138j** with HTIB (Table 20). Acetoxy group *meta* to migrating group can influence the

reaction by negative inductive effect. To our delight, the desired ring contraction product **16j** was successfully obtained in 47% yield using TFE/DCM (1:4) as solvent (entry 1). Using pure TFE, the yield of acetal **16j** increased to 66% (entry 2). The deprotection of substrate **138j** into phenol **88j** was observed when MeOH was used as solvent (entry 3).

Table 20. Reactions of oxygenated substrate **138j** with HTIB

Entry	Solvent	Time	Product (% Yield)
1	TFE/DCM (1:4)	5 min	16j (47) ^b
2	TFE	5 min	16j (66)
3	MeOH	5 h	88j (55)

a) Isolated yield. b) Preliminarily test was performed by Rafael Ribeiro da Silva Soares

With the optimized conditions, ring contraction was successfully carried out in a variety of oxygenated substrates (Table 21). Benzoyl protected alkene **138s** gave acetal **16s** in 71% yield (entry 1). Acetyl protected alkene **138k** smoothly afforded product **16k** in 60% yield (entry 2). In contrast to 6-acetamide alkene **1p** (Table 19), 6-acetyl alkene **138c** gave acetal **16c** in 65% yield (entry 3).

Table 21. Reactions of oxygenated alkenes **138s**, **138k** and **138c** with 1.2 equiv of HTIB

Entry	Substrate	Conditions	Product (Yield%) ^a
1	138s	TFE, 0 °C, 5 min	16s (71%)
2	138k	TFE, 0 °C, 5 min	16k (60%)
3	138c	TFE, 0 °C, 5 min	16c (65%)

a) isolated yield

All the ring contraction trifluoroethoxy acetal indane were characterized by ¹H NMR and ¹³C NMR data. The representative values of acetal hydrogens and carbons are given below (**Figure 33**). The characteristic coupling constant of acetal hydrogen with adjacent benzylic hydrogen ranges from 8.1 to 8.4 Hz. The acetal hydrogens are found in the range of 4.69 to 4.74 ppm for all acetal compounds. Acetal carbons are observed at 105.0 or at 105.1 ppm. The two OCH₂ group give two quartet signals at 61.8 and at 63.3 ppm with coupling constant of 34.8 Hz showing its coupling with three fluorine atoms of CF₃ group. The quaternary carbons attached to the fluorines appear as quartets with coupling constant of 276 Hz at 123.69 and at 123.74 ppm.

Figure 33. Characteristic ¹H NMR and ¹³C NMR values of acetals **16c**, **16j**, **16k** and **16s**

To have a racemic standard for analysis by HPLC and/or GC using chiral stationary phase, *trans*-indanes **7f** and **7b** were prepared according to reported protocol in 36% and 62% yield, respectively (Table 22, entries 1 and 2).²⁷ Using TFE, 1-aryl substituted alkene **1f** gave *trans*-indane **16f** in diastereoselective fashion in 63% yield (entry 3). In this case, better yield but low diastereoselectivity was observed when compared to reaction carried out in MeOH (entry 1 and 3). When compared to reaction in MeOH, alkenes **1b** in TFE resulted in *trans*-indanes **16b** in similar yield but in lower diastereoselectivity (entry 1 and 4).²⁷ The desired acetal **16a** was obtained in good yield when alkene **1a** was treated with HTIB in pure TFE (entry 5).²⁷ To obtain hydroxy functionalized indane **17f**, HFIP/DCM was used together with a small amount of water to minimize the formation of undesired acetal-like product.²⁷ The aldehyde formed in this process was reduced *in situ* with NaBH₄ to obtain corresponding indane **17f** in better yield and diastereomeric ratio than in MeOH and TFE (entries 1, 3 and 6). In similar fashion, *trans*-indane **17b** was isolated from 1-methyl alkene **1b** in similar yield to that of MeOH and TFE but in lower diastereomeric ratio than in MeOH (entries 2, 4 and 7).

Table 22. Reactions of alkenes **1a**, **1b** and **1f** with HTIB

Entry	Substrate	Conditions	Product (Yield) ^a
1		3.6 equiv HTIB, MeOH 0 °C to rt, 5 h	7f (36%)
2		2 equiv HTIB, MeOH 0 °C to rt, 4 h	7b (62%)
3		TFE/DCM (1:4) 0 °C, 5 min	16f (63%) <i>d.r.</i> 20:1
4		TFE/DCM (1:4) 0 °C, 5 min	16b (63%) <i>d.r.</i> 12:1
5		TFE, 0 °C, 5 min	16a (72%)
6		i) HFIP/DCM (1:4), 22 equiv H ₂ O, 0 °C, 5 min ii) NaBH ₄ , rt, 2 h	17f (68%)
7		i) HFIP/DCM (1:4), 22 equiv H ₂ O, 0 °C, 5 min ii) NaBH ₄ , rt, 2 h	17b (62%) <i>d.r.</i> 13:1

a) Isolated yield

The significant ^1H and ^{13}C NMR data of acetal indanes are given below (**Figure 34**). The acetal hydrogens with coupling constant of 6.9 and 7.5 Hz at 4.35 ppm and at 4.27 ppm are observed for compounds **7f** and **7b**, respectively. The acetal carbons show peaks at 107.0 ppm. Similarly, the acetals hydrogens for fluorinated compounds **16a**, **16b** and **16f** give signals between 4.64 to 4.73 ppm with coupling constant ranges from 7.8 to 8.4 Hz. The methylene hydrogens next to hydroxyl group appear as doublets at 3.80 and at 3.71 ppm in ^1H NMR for compound **17f** and **17b**, respectively. The ^{13}C NMR peaks at 65.9 and 66.1 ppm are assigned to methylene hydrogen adjacent to hydroxyl group for compounds **17f** and **17b**, respectively.

Figure 34. Characteristic ^1H NMR and ^{13}C NMR values of **7b**, **7f**, **16a**, **16b**, **16f**, **17b** and **17f**

The oxidative rearrangement of olefins was investigated in depth with HTIB. Different cyclic alkenes, substituted with oxygen, with nitrogen, or at position 1 with aryl or methyl undergoes ring contraction reaction giving indanes as acetal or as alcohol in good to high yield.

3.2.3 Oxidative rearrangement of alkenes using *in situ* generated hypervalent iodine(III)

The development of reactions using *in situ* generated hypervalent iodine species is one of the most notable achievements in the area.^{18,48,50,125-127} In this section, we describe a flexible and general strategy developed for *in situ* generation of HTIB and its use in the oxidative rearrangement of alkenes. HTIB is formed from the inexpensive reagents iodobenzene, *m*CPBA and TsOH.H₂O.

Fluoroalcohols, like TFE and HFIP, exhibit unique properties like high polarity, low nucleophilicity, high ionizing power and exceptional hydrogen-bond donor ability. Moreover, TFE and HFIP have the capability to stabilize reactive cationic intermediates which may be produced by hypervalent iodine species.^{39,128,129} Using the TFE and HFIP as solvents and cyclic alkene **87a** as substrate, several alternatives to perform an oxidative rearrangement were investigated. The reaction was performed in three steps. First, HTIB was generated *in situ* by treating iodobenzene with *m*CPBA and TsOH.H₂O at room temperature in a mixture of TFE and DCM.^{130,131} Second step involved the addition of the appropriate solvent (HFIP/DCM) for the oxidative rearrangement, followed by addition of substrate **87a**. The presence of a small amount of water minimizes the formation of undesired acetal-like product.²⁷ The aldehyde formed in this process was reduced *in situ* with NaBH₄, forming the corresponding hydroxy ring contraction product **191a** in 63% yield (Table 23, entry 1). Removal of the solvent after formation of the iodine(III), gave the desired product **191a** in a similar yield (entry 2). The effect of solvents on the model reaction was further examined. Using a 1:1 mixture of TFE/DCM and different amounts of H₂O afforded the desired alcohol **191a** in low to moderate yield (entries 3-6). Using a smaller amount of TFE gave alcohol **191a** in 56% yield (entry 7). The use of the highly polar and less nucleophilic solvent HFIP in different mixtures with DCM and H₂O gave the ring contraction product **191a** in good yields (entries 8-11). The best yield was obtained when 1:6 ratio of HFIP/DCM was used, in the presence of H₂O. This yield is comparable to that obtained using commercially available HTIB (entry 11). The desired reaction failed to take place when DCM/H₂O was used (entry 12). We also considered the use of other

oxidants, like Oxone® (KHSO_5),^{14,132,133} hydrogen peroxide (H_2O_2),⁵⁰ and potassium persulfate ($\text{K}_2\text{S}_2\text{O}_8$).¹³⁴ Oxone® was tested using different solvents (CH_3CN , TFE/DCM, and CHCl_3) without success (entries 13-15). Starting material was recovered when $\text{K}_2\text{S}_2\text{O}_8$ and H_2O_2 were used as oxidants (entries 16 and 17).

Table 23. Rearrangement reactions of cyclic alkene **87a** using *in situ* generated HTIB

Entry	Oxidant	Solvent step i	Solvent step ii	Yield%
1	<i>m</i> CPBA	TFE/DCM (1:1)	HFIP/DCM (1:4), 22 equiv H_2O	63
2	<i>m</i> CPBA	TFE/DCM (1:1) (evap.)	HFIP/DCM (1:4), 22 equiv H_2O	64
3	<i>m</i> CPBA	TFE/DCM (1:1)	22 equiv H_2O	48
4	<i>m</i> CPBA	TFE/DCM/ H_2O (1:1:1)	-	23
5	<i>m</i> CPBA	TFE/DCM (1:1)	H_2O (1 mL)	57
6	<i>m</i> CPBA	TFE/DCM (1:1)	H_2O (2 mL)	31
7	<i>m</i> CPBA	TFE/DCM (1:6)	22 equiv H_2O	56
8	<i>m</i> CPBA	HFIP/DCM/ H_2O (1:3:3)	-	47
9	<i>m</i> CPBA	HFIP/DCM (1:1)	22 equiv H_2O	61
10	<i>m</i> CPBA	HFIP/DCM/ H_2O (1:6:6)	-	54
11	<i>m</i>CPBA	HFIP/DCM (1:6)	22 equiv H_2O	71(65)^b
12	<i>m</i> CPBA	DCM/ H_2O (1:1)	-	- ^c
13	Oxone®	CH_3CN	HFIP/DCM (1:4), 22 equiv H_2O	- ^c
14	Oxone®	TFE/DCM (1:1)	HFIP/DCM (1:4), 22 equiv H_2O	27
15	Oxone®	CHCl_3	HFIP/DCM (1:4), 22 equiv H_2O	11 ^c
16	$\text{K}_2\text{S}_2\text{O}_8$	TFE/DCM (1:6)	22 equiv H_2O	- ^c
17	H_2O_2	H_2O_2 , TFE/DCM (1:1)	22 equiv H_2O	- ^c

^a Isolated yields,

^b Reaction carried out with commercially available Koser's reagent.

^c Starting material recovered.

The use of 1,4-diiodobenzene instead of iodobenzene was also investigated. When the oxidative rearrangement of **87a** was carried out with this new Koser's reagent derivative, the rearrangement product **191a** was obtained in 63% yield (**Scheme 53**).

Scheme 53

Based on the previous work, we know that alkyl substituted double bonds can have a different reactivity in rearrangements.^{28,36,135} Thus, a second screening was performed with alkene **1aa**. Under the optimized reaction conditions for **87a**, the desired ring contraction product **15aa** was obtained in only 41% yield (Table 24, entry 1). Using a mixture of TFE/DCM as a solvent enhanced the yield to 73% (entry 2). However, if the substrate is added together with *m*CPBA, another oxidized product, 1-methyl-2-tetralone (**209aa**), was obtained (entry 3). This transformation also took place in the presence of a catalytic amount of PhI (entry 4) or without it (entry 5).

Table 24. Rearrangement reactions of 1,2-dihydro-4-methylnaphthalene (**1aa**)

Entry	Reagents and Conditions	Product (%Yield) ^a
1	i) 1.2 equiv (PhI, <i>m</i> CPBA, TsOH.H ₂ O), HFIP/DCM (1:6); ii) 1aa	15aa (41) ^b
2	i) 1.2 equiv (PhI, <i>m</i> CPBA, TsOH.H ₂ O), TFE/DCM (1:1); ii) 1aa	15aa (73) ^c
3	1aa , 1.2 equiv (PhI, <i>m</i> CPBA, TsOH.H ₂ O), TFE/DCM (1:4)	209aa (73)
4	1aa , PhI 30 mol%, 1.2 equiv (<i>m</i> CPBA, TsOH.H ₂ O), TFE/DCM (1:4)	209aa (75) ^c
5	1aa , 1.2 equiv (<i>m</i> CPBA, TsOH.H ₂ O), TFE/DCM (1:4),	209aa (81)

a) Isolated yield. b) Performed by Paulo Scarassati. c) Performed by Nazli Jalalian

This one step transformation of **1aa** into **209aa** is fast, convenient, high yielding, and uses readily available chemicals, constituting a useful method to obtain 2-tetralones (**209aa**). Analogous two-step protocols were also reported.^{136,137} Additionally, compounds like **209aa** can be obtained by the rearrangement of epoxides using Lewis acids.¹³⁷⁻¹⁴⁰ Another route to transform **1aa** into **209aa** is through a hydroboration/oxidation sequence.¹⁴¹

The mechanism for the epoxidation and rearrangement of **1aa** is given below (**Scheme 54**).¹⁴² The electrophilic attack of π electron of alkene **1aa** on oxygen atom of *m*CPBA (**210**) gives epoxide **212** via transition state **211**. Proton transfer followed by ring opening leads to intermediate **215**. The 1,2-hydride shift results in formation of rearrangement product **209aa**.

Scheme 54. Mechanism of epoxidation/rearrangement of **1aa**

Having established the optimal reaction condition for the *in situ* generation of HTIB, the scope of the oxidative rearrangement of alkenes was systematically examined (Table 25).

Table 25. Oxidative rearrangement of alkenes using *in situ* generated iodine(III)

Step i:		Step ii:		Step iii:	
$\text{PhI} \xrightarrow[\text{solvent}]{\text{mCPBA, TsOH.H}_2\text{O}}$		$\text{Substrate} \xrightarrow{\text{solvent}}$		$\text{rearrangement product} \xrightarrow{\text{NaBH}_4}$	
PhI(OH)OTs				reduced product	
Entry	Substrate	Conditions	Product	Yield ^{a,b}	
1		i) 1.2 equiv (PhI, <i>m</i> CPBA TsOH.H ₂ O) HFIP/DCM (1:6), 30 min ii) 22 equiv H ₂ O, 87b , 2 min iii) NaBH ₄ , 2 h		83 (87)	
2		i) 1.2 equiv (PhI, <i>m</i> CPBA TsOH.H ₂ O) HFIP/DCM (1:6), 30 min ii) 22 equiv H ₂ O, 1a , 2 min iii) NaBH ₄ , 2 h		65 (74)	
3		i) 1.2 equiv (PhI, <i>m</i> CPBA TsOH.H ₂ O) TFE/DCM (1:1), 30 min ii) 87aa , 5 min		79 (62)	
4		i) 1.2 equiv (PhI, <i>m</i> CPBA TsOH.H ₂ O) TFE/DCM (1:1), 30 min ii) 87bb , 10 min		61 (58)	
5		i) 1.2 equiv (PhI, <i>m</i> CPBA TsOH.H ₂ O) HFIP/DCM (1:6), 30 min ii) 22 equiv H ₂ O, 139 , 2 min		97 (99)	
6		i) 1.2 equiv (PhI, <i>m</i> CPBA TsOH.H ₂ O) HFIP/DCM (1:6), 30 min ii) 22 equiv H ₂ O, 217 , 2 min		81 (84)	

a) Isolated yield. b) Reported yield using commercially available Koser's reagent in brackets.

As shown in Table 25, the reaction conditions are general. Dihydrobenzo[*b*]oxepine **87b** afforded the corresponding chromane **191b** in 83% yield (entry 1). A smooth oxidation took place with 1,2-dihydronaphthalene (**1a**) leading to the indane **17a** (entry 2). The methyl substituted olefins **87aa** and **87bb** were successfully transformed into the corresponding rearrangement products **195aa** and **195bb**, respectively (entries 3 and 4). The exocyclic alkene **139** gave the corresponding ring expansion product **216** in nearly quantitative yield (entry 5).

The generality of methodology was further demonstrated by the oxidative rearrangement of α -methylstyrene (**217**) into the corresponding α -aryl ketone **218** in 81% yield (entry 6). It is important to note that all yields are in the same range of that obtained using commercially available HTIB.

A plausible mechanism for the ring expansion induced by HTIB is presented in **Scheme 55**.^{23,27,30} The electrophilic attack of iodine(III) on the double bond forms benzylic carbocation intermediate **219**. Nucleophilic attack of water molecule at benzylic carbon generates intermediate **220**. The migration of an aryl bond and elimination of PhI and H₂O molecules gives the ring expansion intermediate **221**. Deprotonation leads to product **216**.

Scheme 55. Ring expansion mechanism of **139** mediated by HTIB in HFIP/DCM

The characteristic ¹H and ¹³C NMR spectroscopic data for the rearranged products are given below (**Figure 35**). The NMR spectral data for compounds **191b** and **195aa** is already discussed in **Figure 29**. The hydroxyl hydrogens give broad singlets at 1.54 and 1.56 ppm for compounds **191a** and **17a**, respectively. The methylene carbons in the vicinity of hydroxy group in ¹³C NMR spectrum are found at 66.1 and 66.0 ppm for compound **191a** and **17a**, respectively.^{27,143} The characteristic signals for carbonyl carbons are observed for ketones **15aa**, **216**, **218** and **209aa** at 208.7, at 208.6, at 206.2, at 212.3 ppm, respectively.^{23,27,30}

Figure 35. Characteristics ^1H NMR and ^{13}C NMR data of **191a**, **17a**, **15aa**, **216**, **218** and **209aa**

3.3 Asymmetric Ring contraction reactions mediated by chiral iodine(III)

We envisioned a protocol where the required hypervalent iodine species would be prepared *in situ* from a readily available chiral aryl iodide.^{125,126,144} Thus, iodides **36a**, **36i**, **36m** and **36o-36r** were prepared in an expedited manner using as chiral sources the cheap natural compounds (–)-menthol and (–)-ethyl lactate (**Figure 36**)

Figure 36. Chiral aryl iodide reagents

The screening was performed investigating the behavior of 1,2-dihydronaphthalene (**1a**) under different conditions. Based on our previous experience,¹⁴⁴ *m*CPBA in the presence of TsOH.H₂O was selected for the *in situ* oxidation of iodobenzene derivatives **36a**, **36i**, **36m** and **36o-36r** into the corresponding chiral iodine(III), which would promote the desired oxidative rearrangement. After generation of iodine(III) species, substrate **1a** and water were added. To facilitate purification and analysis, aldehyde **208a** (when formed) was reduced *in situ* by NaBH₄. Two solvent mixtures (1:4 TFE/DCM and 1:4 HFIP/DCM) were used for testing the iodobenzene derivatives **36a**, **36i**, **36m** and **36o-36r**, because either the oxidation of

iodobenzene or the ring contraction have been reported in those solvents.^{27,130} The chiral aryl iodide **36m** afforded alcohol **17a** in 6-7% *ee*. (Table 26, entries 1 and 2). With menthol based aryl iodides **36o** and **36p** nearly a racemic mixture was obtained (entries 3-6). Amide based "one arm" **36p** and **36r** proved ineffective under the conditions tested (entries 7-10). The desired indane **17a** was isolated in 14-15 % *ee* and in good yield with "two arms" C₂-symmetrical chiral aryl iodide **36a** (entries 11-12). A similar *ee*, but lower yield was observed when the two arms amide **36i** was used (entries 13-14). Based on the above results, (*R,R*)-**36a** was selected for additional screening. Increasing the ratio of the fluorinated solvent (TFE or HFIP) resulted in lower *ee* (entries 15-16). Without acid, ring contraction product was not isolated in pure form (entry 17). A considerable increase in *ee* was observed when (+)-camphorsulfonic acid (CSA) was used instead of TsOH.H₂O (entry 18). This might be due to the bulky structure of (+)-CSA when compared to TsOH.H₂O. An increasing trend in *ee* was observed decreasing the ratio of HFIP in HFIP/DCM system from 1:10 to 1:40 (entries 19-21). Using only DCM, none ring contraction product was isolated (entry 22). The desired alcohol **17a** was isolated in 34% yield and 60% *ee* when the temperature was lowered to -78 °C (entry 23, GC chromatograms p. 415-416). However, using TFE/DCM in 1:40 ratio, the desired alcohol **17a** was obtained together with acetal **16a** in 58 and 57% *ee*, respectively (entry 24). Using a higher ratio of TFE, only the acetal **16a** was isolated in 60% yield and 58% *ee* (entry 25, HPLC chromatograms, p. 399 and 400). Lower *ee* was observed when 1:1 mixture of TFE/DCM was used (entry 26). Increasing the ratio of HFIP resulted in lower *ee* of the product **17a** (entry 27). After the above experiments, we selected the condition of entry 25 for further investigation.

Table 26. Asymmetric ring contraction of 1,2-dihydronaphthalene (**1a**).

Entry	Ar*I	Solvent	Acid	Temp	Product (Yield, <i>ee</i>) ^{a, b, c}
1	36m	HFIP/DCM (1:4)	TsOH.H ₂ O	0 °C	17a (43, 7)
2	36m	TFE/DCM (1:4)	TsOH.H ₂ O	0 °C	17a (41, 6)
3	36o	TFE/DCM (1:4)	TsOH.H ₂ O	0 °C	17a (8, 5)
4	36o	HFIP/DCM (1:4)	TsOH.H ₂ O	0 °C	17a (-, 4)
5	36p	HFIP/DCM (1:4)	TsOH.H ₂ O	0 °C	17a (37, 6)
6	36p	TFE/DCM (1:4)	TsOH.H ₂ O	0 °C	17a (32, 8)
7	36q	HFIP/DCM (1:4)	TsOH.H ₂ O	0 °C	-
8	36q	TFE/DCM (1:4)	TsOH.H ₂ O	0 °C	-
9	36r	HFIP/DCM (1:4)	TsOH.H ₂ O	0 °C	-
10	36r	TFE/DCM (1:4)	TsOH.H ₂ O	0 °C	-
11	36a	TFE/DCM (1:4)	TsOH.H ₂ O	0 °C	17a (53, 14)
12	36a	HFIP/DCM (1:4)	TsOH.H ₂ O	0 °C	17a (49, 15)
13	36i	HFIP/DCM (1:4)	TsOH.H ₂ O	0 °C	17a (30, 15)
14	36i	TFE/DCM (1:4)	TsOH.H ₂ O	0 °C	17a (33, 13)
15	36a	TFE/DCM (1:1)	TsOH.H ₂ O	0 °C	17a (51, 6)
16	36a	HFIP/DCM (1:1)	TsOH.H ₂ O	0 °C	17a (53, 8)
17	36a	TFE/DCM (1:1)	-	0 °C	17a (-, 4) ^d
18	36a	HFIP/DCM (1:4)	(+)-CSA	0 °C	17a (54, 25)
19	36a	HFIP/DCM (1:10)	(+)-CSA	0 °C	17a (47, 31)
20	36a	HFIP/DCM (1:20)	(+)-CSA	0 °C	17a (44, 38)
21	36a	HFIP/DCM (1:40)	(+)-CSA	0 °C	17a (36, 42)
22	36a	DCM	(+)-CSA	0 °C	-
23	36a	HFIP/DCM (1:40)	(+)-CSA	-78 °C	17a (34, 60)
24	36a	TFE/DCM (1:40)	(+)-CSA	-78 °C	16a (34, 57), 17a (20, 58)
25	36a	TFE/DCM (1:4)	(+)-CSA	-78 °C	16a (60, 58) ^{e, f}
26	36a	TFE/DCM (1:1)	(+)-CSA	-78 °C	16a (62, 46) ^{e, f}
27	36a	HFIP/DCM (1:10)	(+)-CSA	-78 °C	17a (42, 38) ^e

a) isolated yield; b) *ee* determined by GC and HPLC using chiral column; c) The absolute configuration of **1a** was assigned based on literature value for its optical rotation;¹⁴⁵ d) complex mixture e) step i, TFE/DCM (1:40), 30 min then solvent was removed under reduced pressure; f) no addition of NaBH₄

When (*S,S*)-**36a** (prepared from (+)-ethyl lactate) was used, acetal (–)-**16a** was isolated in similar yield and *ee* (Compare entry 1, Table 27 to entry 25, Table 26, HPLC chromatograms, p. 401-402). After ring contraction, iodide **36a** was easily recovered (84% yield). A similar result was obtained using recovered **36a** (entry 2). CSA could be acting as acid or could also have an influence in the chiral environment. Changes in yield or *ee* were not observed when (–)-CSA was used as acid (entry 3). These results clearly show that the observed stereoinduction is regulated only by chiral aryl iodide **36a**.

Table 27. Asymmetric ring contraction of **1a** using (*S,S*)-**36a**.

<div style="display: flex; align-items: center; justify-content: center;"> <div style="text-align: center; margin-right: 20px;"> <p>1a</p> </div> <div style="text-align: center; margin-right: 20px;"> <p>i) 2.0 equiv ((<i>S,S</i>)-36a, <i>m</i>CPBA), TFE/DCM (1:40), 30 min ii) solvent removed, TFE/DCM (1:4) -78 °C, 5 min</p> </div> <div style="text-align: center; margin-left: 20px;"> <p>(–)-16a</p> </div> </div>		
Entry	Reagents	Yield, <i>ee</i> ^{a,b}
1	(+)-CSA	57, 56
2	(<i>S,S</i>)- 36a recovered and reused, (+)-CSA	56, 55
3	(–)-CSA	56, 55

a) isolated yield; b) *ee* determined by HPLC using chiral column

The reactivity of the *N*-substituted alkene **11** was then investigated. No ring contraction product was isolated when the optimized conditions for **1a** were employed for **11** (Table 28, entries 1 and 2). However, we found that the desired indane **71** could be obtained in 26% yield and 56% *ee* performing the rearrangement step in DCM in the presence of MeOH (entry 3). A slight increase in yield and *ee* was observed when the amount of MeOH was increased to 25 equiv (entry 4). The desired product **71** was isolated in good yield without affecting the *ee* when the ratio of MeOH was further increased (50 and 100 equiv) (entries 5 and 6, HPLC chromatograms p. 394-395). With pure MeOH as solvent, indane **71** was isolated in 55% but in low *ee* (entry 7). The optimized conditions for **11** (entry 5) could be successfully applied for

other nitrogen substituted substrates, such as **1m** and **1o** (entries 8 and 9, HPLC chromatograms, p. 394-396 and 397-398).

Table 28. Asymmetric ring contraction of *N*-substituted alkenes **1l**, **1m** and **1o**

<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p>Step i:</p> <p>Ar*I (<i>R,R</i>)-36a 2.0 equiv</p> <p>2.0 equiv (<i>m</i>CPBA, (+)-CSA), 30 min solvent</p> </div> <div style="text-align: center;"> <p>Step ii:</p> <p>PG-NH- </p> <p>solvent, -78 °C 5 min</p> <p>1l: PG = Ac 1m: PG = Bz 1o: PG = Fmoc</p> </div> <div style="text-align: center;"> <p>Ar*I(OH)CSA</p> <p> </p> <p>7l, 7m and 7o</p> </div> </div>			
Entry	Solvent Step 1	Conditions Step 2 ^a	Product (Yield, <i>ee</i> %) ^{b,c}
1	HFIP/DCM (1:40)	-	Complex mixture
2	TFE/DCM (1:40)	-	Complex mixture
3	TFE/DCM (1:40)	DCM, 8 equiv MeOH	7l (26, 56)
4	TFE/DCM (1:40)	DCM, 25 equiv MeOH	7l (35, 64)
5	TFE/DCM (1:40)	DCM, 50 equiv MeOH	7l (60, 64)
6	TFE/DCM (1:40)	DCM, 100 equiv MeOH	7l (60, 64)
7	TFE/DCM (1:40)	MeOH	7l (55, 12) ^d
8	TFE/DCM (1:40)	DCM, 50 equiv MeOH	7m (71, 58)
9	TFE/DCM (1:40)	DCM, 50 equiv MeOH	7o (75, 58)

a) solvent of step 1 was removed under reduced pressure for entries 3-9; b) isolated yield; c) *ee* determined by HPLC using chiral column; d) time: 6 h

Asymmetric ring contraction was also explored in oxygenated substrates. Several conditions were tested for alkene **138j** (Table 29). Ring contraction product was not isolated using DCM/ 50 equiv MeOH or TFE/DCM (1:40) as solvent (entries 1 and 2). Using a 1:10 or 1:4 ratio of TFE/DCM, indane **16j** was obtained in 61-62% *ee* (entries 3-5). Increasing further the ratio of TFE led to lower *ee* (entry 6). Both yield and *ee* dropped when TFE was used as solvent (entry 7). These results (entries 5-7) were in contradiction with the one obtained for racemic ring contraction reaction where the good yield was acquired when the reaction was run in pure TFE or TFE/DCM (1:4) as solvent and took only 5 min to consume starting material (see section 3.3, Table 20). We thought it might be because of insufficient amount of I*(III) reagent generated *in situ* under the reaction condition. To overcome this problem we generated I*(III) in

TFE/DCM (1:40). Generating the iodine(III) species in TFE/DCM (1:40) and performing the ring contraction in TFE gave indane **16j** in 56% yield, but in only 30% *ee* (entry 8). Higher *ee* and good yield was observed for acetal **16j** when the reaction was carried out in TFE/DCM (1:1) (entry 9). At lower temperature a slightly better result was achieved (entry 10, HPLC chromatograms, p. 409-410). The optimized condition (entry 10) was used to explore the substrate scope of oxygen containing substrates. The treatment of 7-acetoxy alkene **138k** with **36a** resulted in indane **16k** in 41% yield and 78% *ee* (entry 11, HPLC chromatograms, p. 413-414). Similarly, alkene **138c** gave the desired acetal **16c** in good yield and *ee* (entry 12, HPLC chromatograms, p. 405-406). Acetal product **138s** was obtained in 61% yield and 56% *ee* when 8-benzoyl alkene **16s** was subjected to oxidative rearrangement condition (entry 13, HPLC chromatograms, p. 411-412).

Table 29. Asymmetric ring contraction of *O*-substituted alkenes **138c**, **138j**, **138k** and **138s**

Step i:		Step ii:			
$\text{Ar}^*\text{I} \xrightarrow[\text{2.0 equiv}]{\text{2.0 equiv (}m\text{CPBA, (+)-CSA), 30 min evap solvent}} \text{Ar}^*\text{I(OH)CSA}$
		138j , R = 8-OAc 138k , R = 7-OAc 138c , R = 6-OAc 138s , R = 8-OBz			
Entry	Solvent Step 1	Solvent Step 2 ^a	Temp.	Time	Product (Yield, <i>ee</i>) ^{b,c}
1	TFE/DCM (1:40)	DCM/50 equiv MeOH	-78 °C to rt	12 h	Complex mixture
2	TFE/DCM (1:40)	-	-78 °C	6 h	Starting material
3	TFE/DCM (1:10)	-	-78 °C to rt	10 h	16j (32, 61)
4	TFE/DCM (1:10)	-	0 °C	5 min	16j (29, 62)
5	TFE/DCM (1:4)	-	0 °C	5 min	16j (33, 62)
6	TFE/DCM (1:1)	-	0 °C to rt	3 h	16j (34, 46)
7	TFE	-	0 °C to rt	12 h	16j (13, 22)
8	TFE/DCM (1:40)	TFE	0 °C	5 min	16j (56, 30)
9	TFE/DCM (1:40)	TFE/DCM (1:1)	0 °C	5 min	2f (56, 56)
10	TFE/DCM (1:40)	TFE/DCM (1:1)	-40 °C	5 min	16j (58, 64)
11	TFE/DCM (1:40)	TFE/DCM (1:1)	-40 °C	5 min	16k (41, 78)
12	TFE/DCM (1:40)	TFE/DCM (1:1)	-40 °C	5 min	16c (53, 54)
13	TFE/DCM (1:40)	TFE/DCM (1:1)	-40 °C	5 min	16s (61, 56)

a) solvent of step 1 was removed under reduced pressure (entries 1 and 8-13); b) isolated yield; c) *ee* determined by HPLC using chiral column.

The reaction of racemic 1-substituted 1,2-dihydronaphthalenes **1b** and **1f** were also investigated. Starting material (**1f**) was recovered with TFE/DCM (1:1) at -78 °C (Table 30, entry 1). Using TFE/DCM (1:4) as solvent *trans*-indane **16f** was isolated in 34-35% yield and 34-39% *ee* at -40 °C and at -78 °C (entries 2 and 3). Using TFE/DCM (1:1) the acetal **16f** was isolated together with alcohol **17f** in 88% combine yield and in 34-40% *ee* (entry 4, HPLC chromatograms, p. 407-408 and 419-420). This result is superior to that reported in the literature for the same transformation.⁴⁸ Indanes **16f** and **17f** could be used in the synthesis of indatraline, which can be used in the treatment of drug abuse.^{28,47} Good combined yield of **16b** and **17b** and 34-38% *ee* was also obtained for alkene **1b**, although in this case better result was achieved at -78 °C than at -40 °C (entries 5 and 6, HPLC chromatograms, p. 403-404 and 417-418).

Table 30. Asymmetric ring contraction in 1,2-dihydronaphthalenes **1b** and **1f**

Entry	Solvent Step 1	Solvent Step 2 ^a	Temp.	Time	Product (Yield, <i>ee</i>) ^{b,c}
1	TFE/DCM (1:40)	TFE/DCM (1:1)	-78 °C	4 h	Starting material
2	TFE/DCM (1:40)	TFE/DCM (1:4)	-78 °C	2 h	16f (34, 34)
3	TFE/DCM (1:40)	TFE/DCM (1:4)	-40 °C	5 min	16f (35, 39)
4	TFE/DCM (1:40)	TFE/DCM (1:1)	-40 °C	5 min	16f (44, 40), 17f (44, 34) ^d
5	TFE/DCM (1:40)	TFE/DCM (1:1)	-40 °C	5 min	16b (43, 23), 17b (26, 22) ^d
6	TFE/DCM (1:40)	TFE/DCM (1:1)	-78 °C	5 min	16b (43, 38), 17b (34, 34) ^d

a) solvent of step 1 was removed under reduced pressure; b) Isolated yield. c) *ee* determined by HPLC using chiral column. d) Step iii: NaBH₄, 2 h.

The enantiomeric separation of Fmoc-protected acetal indane **7o** was tried with different chiral columns (ASH, ODH, DMP, OJ and OD) and conditions (temp, flow rate and polarity) without success. We planned to convert Fmoc-indane **7o** into acetyl protected indane **7l** (method

already developed for enantiomeric separation) to determine its *ee* (**Scheme 56**). In first step it was deprotected under basic condition of piperidine in DCM.¹⁴⁶ The intermediate amine indane was then protected with acetyl group using Ac₂O and DMAP in Et₃N.²⁷ Acetal **71** was isolated in 77% yield over two steps whereas *ee* was found 58%.

Scheme 56

As we also could not develop a suitable method for the enantiomeric separation of indane **16s** after many attempts we considered of its transformation into acetoxy protected acetal **16j** (**Scheme 57**). The deprotection of benzoyl moiety was achieved with K₂CO₃ in MeOH and water.¹⁴⁷ Using the reported method²⁷ phenolic indane moiety was protected with acetyl group in 90% yield over two step with *ee* of 56%.

Scheme 57

The mechanism for asymmetric ring contraction reaction is shown in **Scheme 58**.^{27,28} Based on the absolute configuration of alcohol **16a**,¹⁴⁵ the electrophilic attack of iodine(III) species occurs selectively on the *Re*-face of double bond forming benzylic carbocation **222**. The nucleophilic attack of CF₃CH₂OH gives intermediate **223**. The necessary *anti*-periplanarity for the rearrangement is achieved via equilibration to its more stable conformational isomer **224**. Migration of the aryl group on **225** gives oxonium **226**. Finally, addition of CF₃CH₂OH leads to acetal **16a**.

Scheme 58. Asymmetric ring contraction reaction of **1a**

The asymmetric synthesis of indanes can be accomplished through the ring contraction of 1,2-dihydronaphthalenes mediated by chiral iodine(III). The ring contraction products are obtained as masked aldehydes which can be converted into a variety of compounds.^{28,120,148-150} The hypervalent iodine species is generated *in situ* from chiral aryl iodide prepared in one high yield step from inexpensive starting material.

4 Conclusion

The behavior of various oxygen-containing benzofused cyclic alkenes such as *2H*-chromenes and 2,3-dihydrobenzo[*b*]oxepine with HTIB was explored.¹⁵¹ *2H*-chromene resulted in substituted *4H*-chromenes together with the *trans*-addition products. Similarly our attempts to execute ring contraction in 4-methyl-*2H*-chromene afforded *cis*-dialkoxy-4-methyl-*2H*-chromane. Ring contraction towards functionalized chromanes and benzofuranes was observed for dihydrobenzoxepines and 2,2-dimethyl-*2H*-chromenes, respectively. This study provides new approaches to obtain a variety of different *O*-heterocycles in 24-87% yield. This methodology is mild and environmentally friendly.

Indanes were synthesized using HTIB. The results showed the tolerance of protecting groups (Ac, Bz and Fmoc) in ring contraction reaction mediated by HTIB. Similarly, oxidative rearrangement was successfully carried out in oxygenated substrates irrespective of their position on aromatic ring.

A novel and general protocol for the oxidative rearrangement of alkenes using *in situ* generated hypervalent iodine(III) was developed.¹⁴⁴ The protocol uses inexpensive, readily accessible, and stable chemicals (PhI, *m*CPBA, TsOH) giving rearrangement products in yields comparable to those obtained using the more expensive commercially available HTIB. Additionally, a new route for the one step transformation of 4-methyl-1,2-dihydronaphthalene into 1-methyl-2-tetralone using *m*CPBA and TsOH was developed. The prepared primary alcohols were subjected to lipase-catalyzed enantioselective acetylation to get chiral non-racemic indanes, chromanes and tetralins (Leandro H. Andrade* and Rodrigo S. Martins).¹⁵²

Finally, we have studied the reactivity of various chiral iodine(III) compounds with 1,2-dihydronaphthalenes. Results obtained demonstrated the practicability of the enantioselective ring contraction using *C*₂-symmetrical chiral iodine(III) derived from lactate ester. The hypervalent iodine species is generated *in situ* from chiral aryl iodine, which is prepared in one

high yield step from inexpensive starting materials. Amine substituted alkenes protected with Ac, Bz and Fmoc groups gave rearranged products in 60-75% yield and 58-64% *ee*. Similarly, oxygen containing substrates (acetyl and benzoyl protected) successfully acetal products in 41-61% yield and 54-78% *ee*. 1-Methyl and aryl substituted alkenes were smoothly transformed into acetal and hydroxy substituted indanes in 77-88% yield and 34-40% *ee*.

5 Experimental Section

All commercially available reagents were used without further purification unless otherwise noted. All solvents used for reactions and chromatography were dried and purified by standard methods.¹⁵³ TLC analyses were performed using silica gel 60F 254 precoated plates, with detection by UV-absorption (254 nm) and by spraying with *p*-anisaldehyde and phosphomolybdic acid solutions followed by charring at ~150 °C for visualization. Flash column chromatography was performed using silica gel 200-400 Mesh. All NMR analyses were recorded using CDCl₃, acetone-d₆ and DMSO-d₆ as solvents and TMS as internal standard. Chemical shifts are reported in ppm downfield from TMS with reference to internal solvent. High-performance liquid chromatography (HPLC) analysis was carried out using Shimadzu LC-20 AT coupled diode array-detector SPD-MA20A and chiral columns of Daicel CHIRALCEL OD-H (4.6 mm x 25 cm), AS-H (4.6 mm x 25 cm) and Sigma Aldrich chiral Astec Cellulose DMP column (4.6 mm x 25 cm). Gas chromatography analysis (GC) was conducted using Shimadzu GC-2010 and chiral column ALPHA DEXTM 120 FUSED SILICA Capillary Column (30m x 0.25mm x 0.25μm). Specific rotation was measured in CH₃Cl and THF with a JASCO P-2000 (589 nm, T = 20 °C, 10 x 100 mm) digital polarimeter.

5.1 Preparation of cyclic olefinic substrates

5.1.1 1,2-Dihydronaphthalene (1a): General procedure reduction/dehydration

To a two neck round bottom flask with magnetic stirrer under nitrogen atmosphere were added NaBH₄ (0.127 g, 3.34 mmol) in anhydrous THF (10 mL) and ketone **85a** (0.657 g, 4.45 mmol). The mixture was stirred for 30 minutes at 0 °C. Anhydrous ethanol (10 mL) was added and the temperature was raised to rt. The temperature was kept the same for another 1 h. The reaction was quenched by addition of distilled H₂O (10 mL) and the mixture was extracted with

EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (2 x 10 mL) and dried over anhydrous MgSO_4 . The solvent was removed under reduced pressure and compound **227** was obtained as white solid (0.640 g, 4.32 mmol, 97%) and used in the next step without purification.

The crude alcohol **227** (0.640 g, 4.32 mmol) was dissolved in toluene (30 mL) with the addition of few crystals of $\text{TsOH} \cdot \text{H}_2\text{O}$ in round bottom flask, fitted with Dean-Stark apparatus. The system was maintained at 130 °C and the reaction was monitored by TLC. The reaction was quenched by addition of saturated solution of NaHCO_3 and extracted with hexane (3 x 30 mL). The combined organic extracts were washed with brine (2 x 10 mL) and dried over anhydrous MgSO_4 . The solvent was removed at reduced pressure and the residue was purified by flash chromatography (hexane), giving compound **1a** (0.505 g, 3.89 mmol, 90%) as colorless oil.²⁷

1,2-Dihydronaphthalene (**1a**)¹⁵⁴

^1H NMR (500 MHz, CDCl_3) δ : 2.31 (m, 2H), 2.80 (t, $J = 8.5$, 2H), 6.02 (dt, $J = 9.5$, 4.5 Hz, 1H), 6.46 (dt, $J = 10$, 2 Hz, 1H), 7.01 (dd, $J = 7$, 1 Hz, 1H), 7.08-7.16 (m, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ : 23.2, 27.5, 125.8, 126.4, 126.8, 127.5, 127.7, 128.6, 134.1, 135.4.

5.1.2 1-Methyl-1,2-dihydronaphthalene (**1b**)

The reaction was performed following the general procedure **5.1.1**, but using ketone **85a** (1.12 g, 7.00 mmol), MeOH (50 mL) and NaBH_4 (0.265 g, 7.00 mmol). After workup, solvent was removed under reduced pressure and alcohol **228** (1.116 g, 6.88 mmol, 98%) was obtained as white solid and used in the next step without purification.

The reaction was performed following the general procedure **5.1.1**, but using alcohol **228** (1.12 g, 6.88 mmol), toluene (40 mL) and $\text{TsOH} \cdot \text{H}_2\text{O}$ (cat. few crystals) at 130 °C. The

crude product was purified by flash column chromatography (1-2 % EtOAc in hexane) giving alkene **1b** (0.920 g, 6.38 mmol, 93%) as colorless oil.²⁸

1-Methyl-1,2-dihydronaphthalene (**1b**)²⁸

¹H NMR (300 MHz, CDCl₃) δ : 1.22 (d, J = 6.9 Hz, 3H), 2.04-2.14 (m, 2H), 2.40-2.50 (m, 2H), 2.91 (sext, J = 7.2 Hz, 1H), 5.92 (dt, J = 9.6, 4.4 Hz, 1H), 6.42 (dt, J = 9.6, 1.8 Hz, 1H), 6.98-7.02 (m, 1H), 7.12-7.14 (m, 3H).

¹³C NMR (75 MHz, CDCl₃) δ : 20.1, 31.2, 31.6, 126.0, 126.1, 126.2, 127.12, 127.14, 127.4, 133.3, 140.4.

5.1.3 4-(3,4-Dichlorophenyl)-3,4-dihydronaphthalen-1(2H)-one (**85f**)

To a stirred solution of 1-naphthol (**89**) (2.00 g, 13.8 mmol) in 1,2-dichlorobenzene (**90**) (1.56 ml, 13.8 mmol) was added anhydrous AlCl₃ (3.68 g, 27.6 mmol). The reaction mixture was heated to 100 °C and stirred at this temperature for 1.5 h. The reaction mixture was then cooled to rt and poured into ice and 1 mol/L HCl (15 mL). The aqueous layer was extracted with DCM (3 x 30 mL). The organic layer washed with H₂O (2 x 20 mL), stirred with Celite (2 g) and activated carbon (2 g) and then filtered. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (5-6 % EtOAc in hexane) giving ketone **85f** (2.80 g, 9.62 mmol, 70%) as a white solid.⁴⁷ MP: 99.4-100.7 (lit. 99-101 °C).¹⁵⁵

4-(3,4-Dichlorophenyl)-3,4-dihydronaphthalen-1(2H)-one (**85f**)⁴⁷

¹H NMR (300 MHz, CDCl₃) δ : 2.20-2.32 (m, 1H), 2.42-2.52 (m, 1H), 2.58-2.77 (m, 2H), 4.28 (dd, J = 8.1, 4.6 Hz, 1H), 6.93-6.97 (m, 2H), 7.23 (d, J = 2.1 Hz, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.39-7.41 (m, 1H), 7.47 (td, J = 7.5, 1.5 Hz, 1H), 8.12 (dd, J = 7.8, 1.5 Hz, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ : 31.6, 36.5, 44.5, 127.4, 127.5, 127.9, 129.3, 130.5, 130.6, 130.9, 132.7, 132.8, 133.8, 144.0, 144.8, 197.3.

5.1.4 1-(3,4-Dichlorophenyl)-1,2-dihydronaphthalene (**1f**)

The reaction was performed following the general procedure **5.1.1**, but using ketone **85f** (2.00 g, 6.90 mmol), MeOH (60 mL) and NaBH_4 (0.265 g, 7.00 mmol). After workup, solvent was removed under reduced pressure and alcohol **229** (1.98 g, 6.75 mmol, 98%) was obtained as white solid and used in the next step without purification.

The reaction was performed following the general procedure as in **5.1.1**, but using alcohol **229** (1.19 g, 6.78 mmol), toluene (30 mL) and $\text{TsOH} \cdot \text{H}_2\text{O}$ (cat. few crystals) at 130 °C. The crude product was purified by flash column chromatography (1-2 % EtOAc in hexane) giving alkene **1f** (1.75 g, 6.36 mmol, 94%) as white solid.⁴⁷ MP: 75.1-75.9 °C (lit. 75.5-75.6 °C).²⁸

1-(3,4-Dichlorophenyl)-1,2-dihydronaphthalene (**1f**)^{28,47}

^1H NMR (300 MHz, CDCl_3) δ : 2.48-2.58 (m, 1H), 2.64-2.74 (m, 1H), 4.08 (t, $J = 8.1$ Hz, 1H), 5.95 (dt, $J = 9.6, 4.4$ Hz, 1H), 6.54 (dt, $J = 9.6, 1.6$ Hz, 1H), 6.81-6.84 (m, 1H), 7.03 (ddd, $J = 8.4, 2.1, 0.6$ Hz, 1H), 7.08-7.13 (m, 2H), 7.18-7.24 (m, 1H), 7.29 (d, $J = 2.1$ Hz, 1H), 7.34 (d, $J = 8.4$ Hz, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ : 31.7, 42.8, 126.39, 126.44, 127.3, 127.5, 127.7, 128.1, 130.21, 130.28, 130.32, 132.3, 133.8, 136.4, 144.9.

5.1.5 6,7-Dihydro-5H-benzo[7]annulene (**87a**)

The reaction was performed following the general procedure **5.1.1**, but using ketone **86a** (3.0 g, 18.75 mmol, THF (20 mL), NaBH_4 (0.532 g, 14.1 mmol), EtOH (15 mL). After workup, solvent was removed under reduced pressure and alcohol **230** was obtained as white solid (2.95 g, 18.2 mmol, 97%) and used in the next step without purification.

The reaction was performed following the general procedure **5.1.1**, but using alcohol **230** (2.95 g, 18.75 mmol), toluene (35 mL) and $\text{TsOH} \cdot \text{H}_2\text{O}$ (cat. few crystals) at 130 °C for 4 h. The crude product was purified by flash column chromatography (hexane) giving benzoannulene **87a** as light yellowish oil (2.48 g, 17.2 mmol, 95%).²⁷

6,7-Dihydro-5H-benzo[7]annulene (87a**)**¹⁵⁶

^1H NMR (200 MHz, CDCl_3) δ : 1.90-2.01 (m, 2H), 2.35-2.49 (m, 2H), 2.81-2.86 (m, 2H), 5.88 (dt, $J = 12.4, 4.6$ Hz, 1H), 6.40 (dt, $J = 12.4, 2$ Hz, 1H), 7.06-7.16 (m, 4H).

^{13}C NMR (75 MHz, CDCl_3) δ : 26.9, 32.4, 36.1, 125.8, 126.5, 128.9, 129.8, 130.8, 132.1, 136.3, 141.6.

5.1.6 2H-Chromene (**1g**)

The reaction was performed following the general procedure **5.1.1**, but using ketone **85g** (1.48 g, 10.0 mmol), THF (10 mL), NaBH_4 (0.28 g, 7.5 mmol), EtOH (10 mL). After workup, solvent was removed under reduced pressure and alcohol **231** was obtained as white solid (1.4 g, 9.6 mmol, 96%) and used in the next step without purification.

The reaction was performed following the general procedure **5.1.1**, but using alcohol **231** (1.4 g, 9.6 mmol), toluene (30 mL) and $\text{PTSA} \cdot \text{H}_2\text{O}$ (cat. few crystals) at 130 °C. The crude

product was purified by flash column chromatography (2% EtOAc in hexane) giving alkene **1g** as light yellowish oil (0.95 g, 7.2 mmol, 75%).²⁷

2*H*-Chromene (**1g**)¹⁵⁷

¹H NMR (200 MHz, CDCl₃) δ : 4.78 (dd, J = 3.4, 1.8, Hz, 2H), 5.72 (dt, J = 10, 3.4 Hz, 1H), 6.38 (dt, J = 9.8, 1.6 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.84 (dd, J = 7.4, 0.8 Hz, 1H), 6.92 (dd, J = 7.4, 1.8 Hz, 1H), 7.07 (td, J = 7.8, 1.8 Hz, 1H).

¹³C NMR (50 MHz, CDCl₃) δ : 65.4, 115.6, 121.2, 121.8, 122.2, 124.4, 126.4, 129.0, 153.9.

5.1.7 2*H*-Thiochromene (**1s**)

The reaction was performed following the general procedure **5.1.1**, but using 4-thiochromanone **85s** (1.48 g, 9.02 mmol), THF (15 mL), NaBH₄ (0.25 g, 6.7 mmol) and EtOH (15 mL). After work up the solvent was removed at reduced pressure and the product alcohol **232** was obtained as yellow solid (1.44 g, 8.73 mmol, 97%) used in the next step without purification.

The reaction was performed following the general procedure **5.1.1**, but using alcohol **232** (0.51 g, 3.1 mmol), toluene (25 mL) and TsOH.H₂O (cat. few crystals) at 130 °C. After workup solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (1% EtOAc in hexane) giving alkene **1s**¹⁵⁸ as light yellowish oil (0.34 g, 2.3 mmol, 75%).²⁷

2*H*-Thiochromene (**1s**)⁵⁹

¹H NMR (200 MHz, CDCl₃) δ : 3.41 (dd, J = 5.2, 1.6 Hz, 2H), 5.89 (dt, J = 10, 5.2 Hz, 1H), 6.45 (dt, J = 10.2, 1.4 Hz 1H), 6.98-7.09 (m, 3H), 7.14-7.19 (m, 1H).

¹³C NMR (50 MHz, CDCl₃) δ : 31.56, 120.69, 122.22, 126.30, 126.39, 126.51, 128.52, 132.05.

5.1.8 2-(3-Methylbut-2-enyl)phenol (**98**)

To a stirred solution of phenol **96** (2.00 g, 21.3 mmol) in anhydrous Et₂O (20 mL) was added Na (0.490 g, 21.3 mmol). This reaction mixture was stirred for 30 min and bromide **97** (2.5 mL, 21.3 mmol) was added. After 2 h, the reaction was quenched by the addition of H₂O. Aqueous phase was extracted with EtOAc (3 x 10 mL), washed with brine (2 x 15 mL) and dried over anhydrous MgSO₄. The crude product was purified by flash column chromatography (5% EtOAc in hexane) giving **98** (2.75 g, 17.0 mmol, 80%) as a light yellowish oil.⁶⁷

2-(3-Methylbut-2-enyl)phenol (**98**)¹⁵⁹

¹H NMR (200 MHz, CDCl₃) δ: 1.77 (s, 6H), 3.35 (d, *J* = 7.2 Hz, 2H), 5.16 (s, 1H), 5.28-5.36 (m, 1H), 6.76-6.81 (m, 1H), 6.87 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.07-7.14 (m, 2H).

¹³C NMR (50 MHz, CDCl₃) δ: 17.8, 25.7, 29.7, 115.7, 120.7, 121.8, 126.8, 127.5, 130.0, 134.7, 154.2.

5.1.9 2,2-Dimethyl-2H-chromene (**1h**) and 2-(prop-1-en-2-yl)-2,3-dihydrobenzofuran (**99**)

To stirred solution of phenol **98** (0.486 g, 3.0 mmol) in DMSO/H₂O (9:1, 20 mL) as solvent was added KHCO₃ (0.33 g, 3.3 mmol) and Pd(dba)₂ (0.086 g, 5 mol%). The reaction was stirred for 3 days at 60 °C in presence of air as a sole reoxidant for Pd. The reaction mixture was filtered from silica pad to remove the Pd catalyst. Aqueous phase was extracted with EtOAc (3 x 10 mL), washed with brine (2 x 15 mL) and dried over anhydrous MgSO₄. The crude product was purified by flash column chromatography (1% EtOAc in hexane) giving inseparable mixture of **1h** and **99** in 2.6:1 ratios (0.285 g, 1.78 mmol, 59%) as colorless oil.⁶⁶

5.1.10 2,3-Dihydro-2,2-dimethylchromen-4-one (**85h**)

To a solution of hydroxyacetophenone **105** (1.13 g, 1.1 mL, 8.3 mmol) in EtOH (absolute, 50 mL), pyrrolidine **107** (1.18 g, 1.36 mL, 16.6 mmol) and acetone (**106**) (4.18 g, 6.08 mL, 83.0 mmol) were added sequentially and the reaction mixture was refluxed overnight. After the completion of reaction monitored by TLC, the reaction mixture was concentrated in *vacuo*. The residue was re-dissolved in DCM and washed with 1 mol/L HCl solution (3x15 mL). After washing with brine (2 x 10 mL), the combined organic layer was dried over anhydrous MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (2% EtOAc in hexane), giving ketone **85h** (1.40 g, 7.95 mmol, 96%) as colorless crystals.⁷⁰ MP: 88-89 °C (lit. 87-89 °C).¹⁶⁰

Dihydro-2,2-dimethylchromen-4-one (85h)⁷⁰

¹H NMR (200 MHz, CDCl₃) δ : 1.46 (s, 6H), 2.73 (s, 2H), 6.93 (d, J = 8.4 Hz, 1H), 7.0 (d, J = 8.4 Hz, 1H), 7.47 (ddd, J = 8.4, 7.8, 1.8 Hz, 1H), 7.86 (dd, J = 7.8, 1.8, 1H).

¹³C NMR (50 MHz, CDCl₃) δ : 26.6, 48.9, 79.2, 118.3, 120.2, 120.7, 126.5, 136.1, 160.0, 192.6.

5.1.11 2,2-Dimethyl-2H-chromene (**1h**)

The reaction was performed following the general procedure **5.1.1**, but using ketone **85h** (1.40 g, 7.95 mmol, NaBH₄ (0.224 g, 5.92 mmol) in anhydrous THF (12 mL) and EtOH (10 mL). The solvent was removed under reduced pressure and the product alcohol **233** was obtained as yellow solid (1.37 g, 7.70 mmol, 97%) used in the next step without purification.

The reaction was performed following the general procedure **5.1.1**, but using alcohol **233** (1.37 g, 7.7 mmol), toluene (35 mL) and TsOH.H₂O (cat. few crystals) at 130 °C. After workup solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (1% EtOAc in hexane) giving alkene **1h** as light yellowish oil (9.76 g, 6.1 mmol, 79%).^{27,28}

2,2-Dimethyl-2H-chromene (**1h**)⁷⁶

¹H NMR (200 MHz, CDCl₃) δ : 1.50 (s, 6H), 5.60 (d, J = 9.8 Hz, 1H), 6.31 (d, J = 9.8, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.84 (dd, J = 7.4, 0.8 Hz, 1H), 6.97 (dd, J = 7.4, 1.6 Hz, 1H), 7.10 (td, J = 7.4, 1.6 Hz, 1H).

¹³C NMR (50 MHz, CDCl₃) δ : 27.9, 76.0, 116.2, 120.6, 121.2, 122.2, 126.2, 129.0, 130.6, 152.9.

5.1.12 4-Phenoxy butanoic acid (**116**)

To the stirred solution of phenol (**96**) (6.58, 70.0 mmol) in acetone (150 ml) in round bottom flask was added potassium carbonate (8.78 g, 70.0 mmol). Reaction was stirred for 30 min. Ethyl 4-bromobutyrate (**115**) (9.94 ml, 70 mmol) was added drop by drop via syringe and catalytic KI was added. It was reflux for 24 h. The reaction mixture was cooled to room temperature and solid was removed by filtration. The solid was washed with acetone (80 ml). The combined filtrate and washings were concentrated under reduce pressure. The residue was taken up in diethyl ether (150 ml), washed with 5 % NaOH (80 ml) and the solvent reduced under reduced pressure. After that the residue was dissolved in EtOH (30 ml) in round bottom flask and treated with 10 % NaOH (130 ml). This reaction mixture was heated at 110 °C for 3 h. The solution was allowed to cool and then acidified with concentrated hydrochloric acid. The

white precipitate formed was filtered and dried to obtain 4-phenoxy butanoic acid (**116**) (10.70 g, 59.44 mmol, 85%) was used in next step without purification.⁶⁰

5.1.13 3,4-Dihydrobenzo[b]oxepin-5(2H)-one (**86b**)

A mixture of 4-phenoxybutanoic acid (**116**) (10 g, 55.5 mmol) and polyphosphoric acid (PPA) (110 g) was heated at 80 °C for 3 h with occasional shaking. The resulting syrup was then poured into ice-water. The product was extracted with EtOAc (3 x 100 mL). After that combined organic layers were washed with 10% NaOH (100 mL), brine (2 x 50 mL), dried over anhydrous MgSO₄ and the solvent was removed under reduced pressure. The product dihydrobenzooxepinone (**86b**) (2.31 g, 14.3 mmol, 26%) was isolated from flash column chromatography (10% EtOAc in hexane) as viscous yellow oil.⁶⁰

3,4-Dihydrobenzo[b]oxepin-5(2H)-one (**86b**)¹⁶¹

¹H NMR (200 MHz, CDCl₃) δ: 2.21 (quint, *J* = 6.8 Hz, 2H), 2.90 (t, *J* = 6.8 Hz, 2H), 4.24 (t, *J* = 6.6 Hz, 2H), 7.09 (t, *J* = 8.4, 2H), 7.38-7.47(m, 1H), 7.77 (d, *J* = 8.4, 1H).

¹³C NMR (50 MHz, CDCl₃) δ: 26.3, 40.6, 72.8, 120.7, 122.7, 129.0, 129.4, 133.7, 162.0, 200.6.

5.1.14 2,3-Dihydrobenzo[b]oxepine (**87b**)

The reaction was performed following the general procedure **5.1.1**, using ketone **86b** (0.98 g, 6 mmol), THF (20 mL), NaBH₄ (0.170 g, 4.5 mmol), EtOH (20 mL). After workup, solvent was removed under reduced pressure and alcohol **234** was obtained as white solid (0.960 g, 5.85 mmol, 96.7%) and used in the next step without purification.²⁷

The dehydration reaction was performed following the general procedure as in **5.1.1**, but using alcohol **234** (0.960 g, 5.85 mmol), toluene (30 mL) and TsOH.H₂O (cat. few crystals)

at 130 °C. The crude product was purified by flash column chromatography (1% EtOAc in hexane) giving alkene **87b** (0.82 g, 5.6 mmol, 96%) as colorless oil.²⁷

2,3-Dihydrobenzo[*b*]oxepine (87b)¹⁶²

¹H NMR (200 MHz, CDCl₃) δ : 2.65 (qd, J = 4.8, 1.6 Hz, 2H), 4.21 (t, J = 4.8 Hz, 2H), 5.99 (dt, J = 11.8, 4.4 Hz, 1H), 6.31 (dt, J = 11.8, 1.8 Hz, 1H), 6.92-6.98 (m, 2H), 7.06-7.17 (m, 2H).

¹³C NMR (50 MHz, CDCl₃) δ : 34.2, 69.5, 119.8, 122.2, 126.7, 127.8, 128.6, 130.1, 132.6, 158.8.

5.1.15 4-Methyl-1,2-dihydronaphthalene (1aa): General procedure Grignard protocol

To a three necks round bottom flask equipped with magnetic stirrer, reflux condenser and N₂ flux was added Mg turnings (0.449 g, 18.5 mmol) and a few crystal of I₂. This mixture was heated with heat gun until violet vapours were observed inside the flask. Dry Et₂O (6 mL) was added to the flask. To this suspension were slowly added MeI (1.16 mL, 18.5 mmol). The system remained under agitation at room temperature for 35 min and then slow addition ketone **85a** (0.803 g, 5.5 mmol) dissolved in anhydrous Et₂O (6 mL). This reaction mixture was kept under stirring for 3 h. Thereafter, it was added HCl (10%) dropwise (until pH acid) and left the reaction to stirred for overnight. The organic layer was extracted with Et₂O (100 mL), washed with Na₂SO₃ (2 x 25 mL), brine (2 x 25 mL) and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (1% EtOAc in hexane) giving compound **1aa** (0.599 g, 4.16 mmol, 76%) as colorless oil.²⁸

4-Methyl-1,2-dihydronaphthalene (1aa)⁷⁵

¹H NMR (200 MHz, CDCl₃) δ : 2.05 (q, J = 1.6 Hz, 3H), 2.17-2.30 (m, 2H), 2.76 (t, J = 8.0 Hz, 2H), 5.82-5.87 (m, 1H), 7.10-7.15 (m, 2H), 7.17-7.24 (m, 2H).

^{13}C NMR (75 MHz, CDCl_3) δ : 19.3, 23.2, 28.4, 122.8, 125.4, 126.3, 126.7, 127.4, 132.3, 135.9, 136.4.

5.1.16 4-Methyl-2H-1-benzopyran (1gg)

The reaction was performed following the general procedure as in **5.1.15**, but using ketone **85g** (2.0 g, 13.5 mmol), Et_2O (70 mL), Mg turnings (0.82 g, 33.75 mmol), MeI (2.1 mL, 33.75 mmol), a crystal of I_2 and HCl (10%). The crude product was purified by flash column chromatography (2% EtOAc in hexane) giving alkene **1gg** (1.50 g, 10.5 mmol, 78%) as colorless oil.²⁷

4-Methyl-2H-1-benzopyran (1gg)⁷⁶

^1H NMR (200 MHz, CDCl_3) δ : 1.98 (q, $J = 1.8$ Hz, 3H), 4.70 (sxt., $J = 1.8$ Hz, 2H), 5.59-5.54 (m, 1H), 6.75-6.91 (m, 2H), 7.05-7.13 (m, 2H).

^{13}C NMR (50 MHz, CDCl_3) δ : 17.8, 65.3, 115.6, 118.3, 121.0, 123.4, 124.2, 128.8, 130.1, 154.1.

5.1.17 2,3-Dihydro-5-methylbenzo[*b*]oxepine (87bb)

The reaction was performed following the general procedure as in **5.1.15**, but using ketone **86b** (0.400 g, 2.74 mmol), Et_2O (20 mL), Mg turnings (0.225 g, 9.24 mmol), MeI (0.58 mL, 9.24 mmol), a crystal of I_2 and HCl (10%). The crude product was purified by flash column chromatography (2% EtOAc in hexane) giving alkene **87bb** (0.383 g, 2.39 mmol, 87%) as colorless oil.¹

2,3-Dihydro-5-methylbenzo[*b*]oxepine (87bb)⁷⁷

^1H NMR (200 MHz, CDCl_3) δ : 2.14 (d, J = 1.4 Hz, 3H), 2.43-2.52 (m, 2H), 4.25 (t, J = 5.8, 2H), 5.95-6.00 (m, 1H), 6.96 (m, 3H), 7.36 (dd, J = 7.4, 2 Hz, 1H).

^{13}C NMR (50 MHz, CDCl_3) δ : 24.6, 31.9, 73.4, 121.0, 122.9, 127.7, 128.5, 131.1, 132.1, 158.4.

5.1.18 2,2,4-Trimethyl-2H-chromene (1hh)

The reaction was performed following the general procedure as in **5.1.15**, but using ketone **85h** (0.785 g, 4.46 mmol), Et_2O (25 mL), Mg turnings (0.364 g, 15.0 mmol), MeI (0.94 mL, 15.0 mmol), a crystal of I_2 and HCl (10%). The crude product was purified by flash column chromatography (2% EtOAc in hexane) giving alkene **1hh** (0.640 g, 3.67 mmol, 83%) as colorless oil.²⁷

2,2,4-Trimethyl-2H-chromene (1hh)⁷⁸

^1H NMR (200 MHz, CDCl_3) δ : 1.38 (s, 6H), 1.98 (d, J = 1.6 Hz, 3H), 5.38 (d, J = 1.4 Hz, 1H), 6.76-6.82 (m, 1H), 6.85-6.89 (m, 1H), 7.06-7.14 (m, 2H).

^{13}C NMR (50 MHz, CDCl_3) δ : 17.9, 28.0, 75.7, 116.3, 120.4, 123.0, 123.2, 127.4, 127.6, 128.9, 152.9.

5.1.19 2,3-Dihydro-2-phenylchromen-4-one (85q)

To a stirred solution of benzaldehyde (**121**) (0.64 g, 0.60 mL, 6.0 mmol) and aniline (**122a**) (0.698 g, 0.9 mL, 7.5 mmol) in MeOH was added 2-hydroxyacetophenone (**105**) (0.817 g, 0.79 mL, 6 mmol) (1.0 mL) and I_2 (0.381 g, 30 mol %, 1.5 mmol) stirred at 40 °C for 72 h. After completion of the reaction (monitored by TLC), the solution was washed with an ice cold saturated $\text{Na}_2\text{S}_2\text{O}_3(\text{aq})$ solution (3x15 mL), extracted with DCM (3x15 mL), washed with brine,

dried over anhydrous MgSO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (3% EtOAc in hexane,), giving ketone **85q** (0.59 g, 2.63 mmol, 53%) as white solid. MP: 70-71 °C (lit. 69-72 °C).¹⁶⁰

2,3-dihydro-2-phenylchromen-4-one (85q)⁷²

^1H NMR (200 MHz, CDCl_3) δ : 2.90 (dd, $J = 17, 3.4$ Hz, 1H), 3.11 (dd, $J = 17, 13$ Hz, 1H), 5.50 (dd, $J = 13, 3.2$ Hz, 1H), 7.02 (m, 2H), 7.38-7.56 (m, 6H), 7.94 (dd, $J = 8.2, 1.8$ Hz, 1H).

^{13}C NMR (50 MHz, CDCl_3) δ : 44.7, 79.6, 118.1, 120.9, 121.6, 126.2, 127.1, 128.8, 128.9, 136.2, 138.7, 161.6, 192.0.

5.1.20 **2,3-Dihydro-2-phenylquinolin-4(1H)-one (130)**

To a solution of *o*-aminoacetophenone (**129**) (0.675 g, 0.6 mL, 5.00 mmol) in MeOH (20 mL), benzaldehyde (**121**) (0.53 g, 0.5 mL, 5.00 mmol) and L-proline (30 mol%, 0.172 g, 1.5 mmol.) were added sequentially and the reaction mixture was allowed to stirred for 48 h at rt. After the completion of reaction monitored by TLC, workup was done with EtOAc (3 x 15 mL), washed with brine (2 x 10 mL), dried over anhydrous MgSO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (3% EtOAc in hexane,) giving ketone **130** (0.73 g, 3.27 mmol, 65%) as colorless crystals.⁷³ MP: 149.2-149.8 °C (lit. 149-150 °C).¹⁶³

2,3-Dihydro-2-phenylquinolin-4(1H)-one (130)^{163,164}

^1H NMR (200 MHz, CDCl_3) δ : 2.74-3.00 (m, 2H), 4.50 (bs, 1H), 4.77 (dd, $J = 13, 4.6$ Hz, 1H), 6.71 (d, $J = 8.4$ Hz, 1H), 6.80 (t, $J = 7.2$ Hz, 1H), 7.31-7.50 (m, 6H), 7.90 (d, 7.8 Hz, 1H).

^{13}C NMR (50 MHz, CDCl_3) δ : 46.5, 58.5, 115.9, 118.5, 119.1, 126.6, 127.6, 128.5, 129.0, 135.4, 141.0, 151.5, 193.2.

5.1.21 1-Acetyl-2,3-dihydro-2-phenylquinolin-4(1H)-one (**85r**)

A solution of ketone **130** (0.233 g, 1.05 mmol) in AcOH/Ac₂O (1:1) (5 mL) was refluxed for 1 h. The reaction mixture was cooled to rt and concentrated under reduced pressure. The crude product was purified by flash column chromatography (25% EtOAc in hexane) giving *N*-acetyl protected ketone **85r** (0.223 g, 0.84 mmol, 81%) as white crystals. MP: 164.7-165.8 °C (lit. 164-165 °C).¹⁶⁵

1-Acetyl-2,3-dihydro-2-phenylquinolin-4(1H)-one (85r**)**¹⁶⁶

¹H NMR (200 MHz, CDCl₃) δ: 2.44 (s, 3H), 3.24 (dd, *J* = 18, 5.4 Hz, 1H), 3.39 (dd, *J* = 18, 2.2 Hz, 1H), 6.47 (bs, 1H), 7.13-7.31 (m, 7H), 7.43-7.51 (m, 1H), 7.93 (dd, *J* = 7.8, 1.6 Hz, 1H).

¹³C NMR (50 MHz, CDCl₃) δ: 23.4, 42.6, 54.7, 125.1, 125.5, 126.1, 126.8, 127.3, 127.5, 128.6, 134.4, 137.9, 141.8, 170.1, 193.1.

5.1.22 *N*-(5-Oxo-5,6,7,8-tetrahydronaphthalen-2-yl)acetamide (**85l**)

To a stirred solution of ketone **136** (0.500 g, 3.10 mmol) and DMAP (0.010 g, 0.080 mmol) in Et₃N (12 mL) was added Ac₂O (1 mL, 10.6 mmol) at rt. After 1 h, the reaction was quenched with MeOH (5 mL) and H₂O (8 mL). The reaction was extracted with EtOAc (3x10), washed with brine (2x10) and dried over anhydrous MgSO₄. Purification by flash column chromatography (40-60% EtOAc in hexane) gave acetyl protected ketone **85l** (0.540 g, 2.45 mmol, 86 %) as a light yellow solid. MP: 124.2-125.5 °C (lit. 124.5-126.7 °C).²⁷

N-(5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)acetamide (**85l**)²⁷

^1H NMR (300 MHz, CDCl_3) δ : 2.06-2.15 (m, 2H), 2.21 (s, 3H), 2.62 (t, $J = 6.6$ Hz, 2H), 2.92 (t, $J = 6$ Hz, 2H), 7.25 (d, $J = 8.4$ Hz, 1H), 7.71 (s, 1H), 7.96 (d, $J = 8.7$ Hz, 1H), 8.24 (s, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ : 23.2, 24.7, 30.0, 38.9, 117.4, 118.4, 128.5, 128.6, 142.5, 146.3, 168.8, 197.5.

5.1.23 *N*-(7,8-Dihydronaphthalen-2-yl)acetamide (**11**)

The reaction was performed following the general procedure **5.1.1**, but using ketone **85I** (0.540 g, 2.66 mmol), MeOH (30 mL) and NaBH_4 (0.113 g, 3.00 mmol). After workup, solvent was removed under reduced pressure and alcohol **235** (0.520 g, 2.54 mmol, 95.0%) was obtained as white solid and used in the next step without purification.

The reaction was performed following the general procedure as in **5.1.1**, but using alcohol **235** (0.520 g, 2.54 mmol), toluene (30 mL) and $\text{TsOH} \cdot \text{H}_2\text{O}$ (cat. few crystals) at 130 °C. The crude product was purified by flash column chromatography (40-60 % EtOAc in hexane) giving alkene **11** (0.390 g, 2.08 mmol, 82%) as white solid. MP: 90.8-91.6 °C (lit. 89.3-90.6 °C).²⁷

N-(7,8-dihydronaphthalen-2-yl)acetamide (**11**)²⁷

^1H NMR (300 MHz, CDCl_3) δ : 2.16 (s, 3H), 2.25-2.33 (m, 2H), 2.78 (t, $J = 8.2$ Hz, 2H), 5.94-5.99 (m, 1H), 6.41 (dt, $J = 9.6, 1.5$ Hz, 1H), 6.95 (d, $J = 8.1$ Hz, 1H), 7.13 (bs, 1H), 7.2 (dd, $J = 8.0, 2.1$ Hz, 1H), 7.32 (s, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ : 22.9, 24.5, 27.6, 117.6, 119.3, 126.2, 127.1, 127.7, 130.6, 136.3, 136.4, 168.1.

5.1.24 *N*-(5-Oxo-5,6,7,8-tetrahydronaphthalen-2-yl)benzamide(**85m**)

To a stirred solution of ketone **136** (0.677 g, 4.20 mmol) and Et₃N (0.65 ml, 0.467 g, 4.62 mmol) in DCM (35 mL) was added BzCl (0.683 ml, 0.826 g, 5.88 mmol). After 3 h, the reaction mixture was washed with 10% HCl, saturated solution of NaHCO₃ and dried over anhydrous MgSO₄.⁷⁹ Purification by flash column chromatography (40-60% EtOAc in hexane) gave benzoyl protected ketone **85m** (0.995 g, 3.75 mmol, 89 %) as a light yellow solid. MP: 193.5-195.2 °C (lit. not reported).

N-(5-Oxo-5,6,7,8-tetrahydronaphthalen-2-yl)benzamide(**85m**)⁸²

¹H NMR (300 MHz, CDCl₃) δ: 2.13 (quin, *J* = 6.3 Hz, 2H), 2.64 (t, *J* = 6.3 Hz, 2H), 2.97 (t, *J* = 6 Hz, 2H), 7.37 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.45-7.52 (m, 2H), 7.55-7.61 (m, 1H), 7.86-7.89 (m, 3H), 8.04 (d, *J* = 8.7 Hz, 1H), 8.11 (d, *J* = 6.9 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ: 23.2, 30.0, 117.8, 118.8, 127.1, 128.6, 128.8, 130.1, 132.2, 134.4, 142.3, 146.3, 165.8, 197.4.

5.1.25 *N*-(7,8-Dihydronaphthalen-2-yl)benzamide (**1m**)

The reaction was performed following the general procedure **5.1.1**, but using ketone **85m** (0.995 g, 3.75 mmol), MeOH (40 mL) and NaBH₄ (0.170 g, 4.50 mmol). After workup, solvent was removed under reduced pressure and alcohol **236** (0.980 g, 3.67 mmol, 98.0%) was obtained as yellowish white solid and used in the next step without purification.

The reaction was performed following the general procedure as in **5.1.1**, but using alcohol **236** (0.980 g, 3.67 mmol), toluene (30 mL) and TsOH.H₂O (cat. few crystals) at 130 °C.

The crude product was purified by flash column chromatography (15-20 % EtOAc in hexane) giving alkene **1m** (0.735 g, 2.95 mmol, 80%) as white solid. MP: 170.2-172 °C (lit. not reported).

***N*-(7,8-dihydronaphthalen-2-yl)benzamide (1m)**⁶⁴

¹H NMR (300 MHz, CDCl₃) δ: 2.30-2.36 (m, 2H), 2.83 (t, *J* = 8.2 Hz, 2H), 5.99 (dt, *J* = 9.2, 4.5 Hz, 1H), 6.45 (dt, *J* = 9.6, 1.8 Hz, 1H), 7.02 (d, *J* = 8.1 Hz, 1H), 7.35 (dd, *J* = 8.1, 2.4 Hz, 1H), 7.46-7.58 (m, 4H), 7.75 (bs, 1H), 7.84-7.88 (m, 2H).

¹³C NMR (75 MHz, CDCl₃) δ: 23.0, 27.7, 117.8, 119.4, 126.3, 126.9, 127.1, 127.9, 128.8, 130.8, 131.8, 135.1, 136.4, 136.6, 165.4.

5.1.26 4-Methyl-*N*-(5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)benzenesulfonamide (85n)

To a stirred solution of ketone **136** (0.161 g, 1.00 mmol) in pyridine (5 ml) was added TsCl (0.191 g, 1.35 mmol). The reaction mixture was heated at reflux for 16 h. The solvent was removed under reduced pressure and the crude residue was extracted with AcOEt (3 x 10) and washed with 1mol/L HCl (10 ml), water (10 mL) and brine (10 mL) and dried over anhydrous MgSO₄.⁸⁰ Purification by flash column chromatography (40-50% EtOAc in hexane) gave tosyl protected ketone **85n** (0.304 g, 0.963 mmol, 96 %) as a white solid. MP: 214.2-215.6 °C (lit. 216-222 °C).⁸³

4-Methyl-*N*-(5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)benzenesulfonamide (85n)⁸³

¹H NMR (300 MHz, CDCl₃) δ: 2.03 (m, 2H), 2.39 (s, 3H), 2.59 (t, *J* = 6.4 Hz, 2H), 2.87 (t, *J* = 6 Hz, 2H), 6.94 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.98-6.99 (m, 1H), 7.15 (bs, 1H), 7.25-7.33 (m, 2H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ: 21.6, 23.1, 29.8, 38.8, 117.2, 118.1, 124.8, 127.2, 129.1, 129.9, 135.9, 141.1, 144.4, 146.3, 197.1.

5.1.27 *N*-(7,8-dihydronaphthalen-2-yl)-4-methylbenzenesulfonamide (**1n**)

The reaction was performed following the general procedure **5.1.1**, but using ketone **85n** (0.788 g, 2.50 mmol), MeOH (30 mL) and NaBH₄ (0.283 g, 7.50 mmol). After workup, solvent was removed under reduced pressure and alcohol **237** (0.761 g, 2.39 mmol, 96.0%) was obtained as yellowish white solid and used in the next step without purification.

The reaction was performed following the general procedure as in **5.1.1**, but using alcohol **237** (0.761 g, 2.39 mmol), toluene (30 mL) and TsOH.H₂O (cat. few crystals) at 130 °C. The crude product was purified by flash column chromatography (15-20 % EtOAc in hexane) giving alkene **1n** (0.542 g, 1.81 mmol, 76%) as white solid (126.7-127.8 °C).

N-(7,8-dihydronaphthalen-2-yl)-4-methylbenzenesulfonamide (**1n**)

¹H NMR (300 MHz, CDCl₃) δ: 2.21-2.29 (m, 2H), 2.37 (s, 3H), 2.69 (t, *J* = 8.4 Hz, 2H), 5.96 (dt, *J* = 9.6, 4.4 Hz, 1H), 6.36 (dt, *J* = 9.6 Hz, 1H), 6.78-6.86 (m, 4H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H).

¹³C NMR (75 MHz, CDCl₃) δ: 21.5 (CH₃), 22.8 (CH₂), 27.4 (CH₂), 119.3 (CH), 121.0 (CH), 126.4 (CH), 126.8 (CH), 127.2 (CH), 128.3 (CH), 129.6 (CH), 131.5 (C), 134.7 (C), 136.1 (C), 136.7 (C), 143.7 (C).

HRMS [ESI(+)] calcd. for [C₁₇H₁₇NO₂S+H]⁺ 300.1053, found 300.1060.

IR (film): 3524, 3257, 3033, 2930, 2883, 2830, 1916, 1735, 1609, 1599, 1575, 1497, 1465, 1397, 1341, 1329, 1314, 1291, 1241, 1209, 1185, 1163, 1124 cm⁻¹.

5.1.28 (9*H*-Fluoren-9-yl)methyl (5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)carbamate (85o)

To a stirred solution of amino ketone **136** (0.484 g, 3.00 mmol) and pyridine (0.29 mL, 3.60 mmol) in anhydrous DCM (25 mL) at 0°C was added solution of Fmoc-Cl (0.854 g, 3.30 mmol) in anhydrous DCM and the resulting reaction mixture was allowed to stir at rt. After 1 h the solution was acidified with 1mol/L HCl. The product was extracted with DCM (3 X 10 mL) and dried over anhydrous Mg₂SO₄.⁸¹ After workup solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (15-25 % EtOAc in hexane) giving Fmoc protected amino ketone **85o** (1.13 g, 2.95 mmol, 98%) as white solid. MP: 160.6-161.5.

(9*H*-Fluoren-9-yl)methyl (5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)carbamate (**85o**)

¹H NMR (300 MHz, CDCl₃) δ: 2.06-2.15 (m, 2H), 2.62 (t, *J* = 6.3 Hz, 2H), 2.91 (t, *J* = 6.0 Hz, 2H), 4.27 (t, *J* = 6.4 Hz, 1H), 4.57 (d, *J* = 6.6 Hz, 2H), 6.95 (bs, 1H), 7.14 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.32 (td, *J* = 7.6, 1.2 Hz, 1H), 7.37-7.44 (m, 3H), 7.56-7.62 (m, 2H), 7.78 (dt, *J* = 7.5, 0.9 Hz, 2H), 7.98 (d, *J* = 8.7 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ: 23.2 (CH₂), 30.0 (CH₂), 38.9 (CH₂), 47.0 (CH), 67.0 (CH₂), 116.4 (CH), 117.0 (CH), 120.1 (CH), 124.8 (CH), 127.1 (CH), 127.8 (CH), 128.1 (C), 128.7 (CH), 141.3 (C), 142.2 (C), 143.5 (C), 146.3 (C), 152.9 (C), 197.3 (C).

HRMS [ESI(+)] calcd. for [C₂₅H₂₁NO₃+H]⁺ 384.1600, found 384.1600.

IR (film): 3305, 3065, 2946, 2890, 1737, 1665, 1602, 1585, 1537, 1495, 1478, 1450, 1427, 1412, 1350, 1336, 1323, 1287, 1219, 1185, 1164, 1129, 1105 cm⁻¹.

5.1.29 (9*H*-Fluoren-9-yl)methyl (7,8-dihydronaphthalen-2-yl)carbamate (**1o**)

The reaction was performed following the general procedure **5.1.1**, but using ketone **85o** (1.15 g, 3.00 mmol), MeOH (50 mL) and NaBH₄ (0.227 g, 6.00 mmol). After workup, solvent was removed under reduced pressure and alcohol **238** (1.12 g, 2.91 mmol, 97.0%) was obtained as white solid and used in the next step without purification.

The reaction was performed following the general procedure as in **5.1.1**, but using alcohol **238** (1.12 g, 2.91 mmol), toluene (50 mL) and TsOH.H₂O (cat. few crystals) at 130 °C. The crude product was purified by flash column chromatography (10-30 % EtOAc in hexane) giving alkene **1o** (0.890 g, 2.42 mmol, 83%) as white solid. MP: 141-142 °C.

(9*H*-Fluoren-9-yl)methyl (7,8-dihydronaphthalen-2-yl)carbamate (**1o**)

¹H NMR (300 MHz, CDCl₃) δ: 2.25-2.33 (m 2H), 2.77 (t, *J* = 8.2 Hz, 2H), 4.27 (t, *J* = 6.6 Hz, 2H), 4.53 (d, *J* = 6.9 Hz, 2H), 5.95 (dt, *J* = 9.6, 4.4 Hz, 1H), 6.41 (dt, *J* = 9.6, 1.6 Hz, 1H), 6.57 (bs, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 7.08-7.18 (m, 2H), 7.32 (td, *J* = 7.4, 1.2 Hz, 2H), 7.38-7.44 (m, 2H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.78 (d, *J* = 7.5 Hz, 2H).

¹³C NMR (75 MHz, CDCl₃) δ: 23.0 (CH₂), 27.7 (CH₂), 47.1 (CH), 66.8 (CH₂), 116.5 (CH), 118.2 (CH), 120.0 (CH), 124.9 (CH), 126.4 (CH), 127.0 (CH), 127.1 (CH), 127.5 (CH), 127.7 (CH), 130.0 (C), 136.1 (C), 136.6 (C), 141.3 (C), 143.7 (C), 153.3 (C).

HRMS [ESI(+)] calcd. for [C₂₅H₂₁NO₂+H]⁺ 368.1651, found 368.1648.

IR (film): 3307, 3030, 2931, 2882, 2826, 1703, 1612, 1585, 1527, 1478, 1465, 1450, 1425, 1326, 1308, 1278, 1219, 1170, 1104 cm⁻¹.

5.1.30 **7-Nitro-3,4-dihydronaphthalen-1(2H)-one (117)** and **5-nitro-3,4-dihydronaphthalen-1(2H)-one (118)**

To a stirred solution of ketone **85a** (1.46 g, 10.0 mmol) in H_2SO_4 (21 mL) at 0 °C was added dropwise HNO_3 (0.62 mL, 10.5 mmol) in H_2SO_4 (3.6 mL) and the solution was stirred for 1 h. The solution was poured into ice/water (15 mL), stirred for another 30 min. The reaction mixture was filtered and washed with H_2O . The solid was dried and purified by flash column chromatography (15-20 % ethyl acetate in hexane) giving 7-nitro-ketone **117** (1.123 g, 5.87 mmol, 59%) as white solid (MP: 103.3-104 °C (lit. 103.5-103.6 °C))³⁷ and 5-nitro-ketone **118** (0.345 g, 1.77 mmol, 18%) (MP: 99-99.6 °C (lit. 98.8-98.9 °C)).³⁷

7-Nitro-3,4-dihydronaphthalen-1(2H)-one (117)³⁷

^1H NMR (300 MHz, CDCl_3) δ : 2.16-2.25 (m, 2H), 2.74 (dd, $J = 7.2$, 6 Hz, 2H), 3.08 (t, $J = 6$ Hz, 2H), 7.46 (dd, $J = 8.4$, 0.4 Hz, 1H), 8.30 (dd, $J = 8.4$, 2.4 Hz, 1H), 8.86 (dd, $J = 2.6$, 0.4 Hz, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ : 22.5, 29.8, 38.6, 122.5, 127.1, 130.3, 133.4, 147.1, 150.8, 195.9.

5-Nitro-3,4-dihydronaphthalen-1(2H)-one (118)³⁷

^1H NMR (300 MHz, CDCl_3) δ : 2.13-2.22 (m, 2H), 2.70-2.75 (m, 2H), 3.22 (t, $J = 6.1$ Hz, 2H), 7.48 (t, $J = 4.5$ Hz, 1H), 8.09 (dd, $J = 8.1$, 1.5 Hz, 1H), 8.35 (dd, $J = 7.8$, 1.5 Hz, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ : 22.2, 26.4, 38.2, 127.0, 128.8, 132.1, 134.5, 138.5, 149.4, 196.

5.1.31 **7-Amino-1,2,3,4-tetrahydronaphthalen-1-ol (119)** and **7-amino-1,2,3,4-tetrahydronaphthalen-1-ol (120)**

To stirred solution of 7-nitro-ketone **117** (0.784 g, 4.1 mmol) in MeOH (50 mL) was added 10% Pd/C (0.090 g) at rt. The mixture was subjected to 6 atm of H₂ for 12 h. The reaction mixture was then filtered through a silica gel pad (200-400 Mesh, ca. 10 cm) and the filtrate was concentrated. The crude product was purified by flash column chromatography (25-50 % EtOAc in hexane) giving 7-amino ketone **119**³⁷ (0.535 g, 3.32 mmol, 81%) as yellowish solid (MP: 91.4-92.4 °C (MP: 137.3-138 °C (lit. 137.7-137.8 °C))³⁷ and 7-amino alcohol **120** (0.088 g, 0.132 mmol, 13%) as a white solid (MP: 91.4-92.4 °C (lit. 91.7-91.8 °C)).³⁷

7-Amino-3,4-dihydronaphthalen-1(2H)-one (119)³⁷

¹H NMR (300 MHz, CDCl₃) δ: 2.05-2.13 (m, 2H), 2.61 (t, *J* = 6.0 Hz, 2H), 2.85 (t, *J* = 6.0 Hz, 2H), 3.70 (bs, 2H), 6.83 (dd, *J* = 8.1, 2.7 Hz, 1H), 7.05 (dd, *J* = 8.1, 0.3 Hz, 1H), 7.32 (dd, *J* = 2.7, 0.3 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ: 23.6, 28.8, 39.2, 112.1, 121.1, 129.6, 133.2, 134.8, 145.0, 198.8.

7-Amino-1,2,3,4-tetrahydronaphthalen-1-ol (120)³⁷

¹H NMR (300 MHz, CDCl₃) δ: 1.65-2.02 (m, 5H), 2.53-2.72 (m, 2H), 3.09 (bs, 2H), 4.62 (t, *J* = 4.9 Hz, 1H), 6.53 (dd, *J* = 8.1, 2.7 Hz, 1H), 6.72 (d, *J* = 2.1 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ: 19.2, 28.3, 32.4, 68.2, 114.7, 115.1, 127.1, 129.6, 139.6, 144.3.

5.1.32 N-(8-Oxo-5,6,7,8-tetrahydronaphthalen-2-yl)acetamide (85p)

The reaction was performed following the general procedure as in **5.1.22**, but using ketone **119** (0.535 g, 3.32 mmol), DMAP (0.010 g, 0.08 mmol) and Ac₂O (1.10 mL, 11.3 mmol) in Et₃N (15 mL). Purification by flash column chromatography (60-100% EtOAc in hexane) gave acetyl protected ketone **85p** (0.635 g, 3.13 mmol, 79 %) as a light yellow solid. MP: 159.8-161.5 °C (lit. 161-161.1 °C).³⁷

N-(8-Oxo-5,6,7,8-tetrahydronaphthalen-2-yl)acetamide (85p)³⁷

^1H NMR (300 MHz, CDCl_3) δ : 2.08-2.16 (m, 2H), 2.22 (s, 3H), 2.62-2.67 (m, 2H), 2.92 (t, J = 6.0 Hz, 2H), 7.22 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 2.1 Hz, 1H), 8.19 (dd, J = 8.4, 2.4 Hz, 1H), 8.82 (bs, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ : 23.2, 24.3, 28.9, 39.0, 117.5, 125.7, 129.4, 132.4, 137.3, 140.1, 169.1, 198.9.

5.1.33 *N*-(5,6-Dihydronaphthalen-2-yl)acetamide (**1p**)

The reaction was performed following the general procedure **5.1.1**, but using ketone **85p** (0.535 g, 3.32 mmol), MeOH (50 mL) and NaBH_4 (0.250 g, 6.64 mmol). After workup, solvent was removed under reduced pressure and alcohol **239** (0.635 g, 3.10 mmol, 93%) was obtained as white solid and used in the next step without purification.

The reaction was performed following the general procedure as in **5.1.1**, but using alcohol **239** (0.205 g, 1.00 mmol), toluene (10 mL) and $\text{TsOH} \cdot \text{H}_2\text{O}$ (cat. few crystals) at 130 °C. The crude product was purified by flash column chromatography (20-40 % ethyl acetate in hexane) giving alkene **1p** (0.184 g, 0.982 mmol, 98%) as white solid. MP: 52.1-53.9 °C (lit. 51.2-54.6 °C).³⁷

N-(5,6-Dihydronaphthalen-2-yl)acetamide (**1p**)³⁷

^1H NMR (300 MHz, CDCl_3) δ : 2.15 (s, 3H), 2.26-2.33 (m, 2H), 2.74 (t, J = 8.1 Hz, 2H), 6.01-6.07 (m, 1H), 6.41 (dt, J = 9.6, 1.5 Hz, 1H), 7.03 (d, J = 7.5 Hz, 1H), 7.18-7.22 (m, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ : 23.2, 24.5, 26.8, 117.7, 118.3, 127.5, 127.8, 129.3, 131.5, 134.6, 136.1, 168.2.0.

5.1.34 7,8-Dihydronaphthalen-1-ol (**88j**)

The reaction was performed following the general procedure **5.1.1**, but using ketone **85j** (0.892 g, 5.50 mmol), MeOH (40 mL) and NaBH₄ (0.208 g, 5.50 mmol). After workup, solvent was removed under reduced pressure and alcohol **240** (0.885 g, 5.39 mmol, 98.0%) was obtained as white solid and used in the next step without purification.³⁷

The crude alcohol **241** (0.885 g, 5.39 mmol), dissolved in anhydrous THF (10 mL) was added with H₃PO₄ (6 ml). The system was maintained at 80 °C and the reaction was monitored by TLC. The reaction was quenched by addition of saturated solution of NaHCO₃ and the mixture was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine and dried over anhydrous MgSO₄. The solvent was removed at reduced pressure and the residue was purified by flash chromatography (10-15 % ethyl acetate in hexane), giving alkene **88j** (0.614 g, 4.20 mmol, 78%) as white solid. MP: 66-67 °C (lit. 53.3-54.6 °C¹⁶⁷ and 73.5-74.5 °C³⁷).

7,8-Dihydronaphthalen-1-ol (**88j**)³⁷

¹H NMR (300 MHz, CDCl₃) δ : 2.29-2.37 (m, 2H), 2.76 (t, J = 8.4 Hz, 2H), 4.67 (s, 1H), 5.98-6.05 (m, 1H), 6.40 (dt, J = 9.6, 2.1 Hz, 1H), 6.65 (d, J = 8.1 Hz, 2H), 7.02 (t, J = 7.8 Hz, 1H)

¹³C NMR (75 MHz, CDCl₃) δ : 19.5, 22.6, 114.5, 119.1, 120.5, 126.8, 127.6, 128.6, 135.4, 152.0.

5.1.35 7,8-Dihydronaphthalen-1-yl acetate (**138j**)

The reaction was performed following the general procedure as in **5.1.22**, but using alkene **88j** (0.614 g, 4.20 mmol), DMAP (0.015 g, 0.12 mmol) and Ac₂O (1.50 ml, 15.90 mmol) in Et₃N (16 mL) at rt. Purification by flash column chromatography (3-5% EtOAc in hexane) gave acetyl protected alcohol **138j** (0.760 g, 4.046 mmol, 96 %) as a colorless liquid.²⁷

7,8-Dihydronaphthalen-1-yl acetate (138j)⁸⁷

¹H NMR (300 MHz, CDCl₃) δ : 2.25-2.32 (m, 2H), 2.31 (s, 3H), 2.64 (t, J = 8.2 Hz, 2H), 6.04 (dt, J = 9.6, 4.4, Hz, 1H), 6.46 (dt, J = 9.6, 1.8 Hz, 1H), 6.86 (dd, J = 8.1, 1.2, Hz, 1H), 6.9 (d, J = 7.2 Hz, 1H), 7.14 (t, J = 8.1 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ : 20.6, 20.7, 22.3, 120.6, 123.7, 126.7, 126.9, 127.3, 128.9, 135.6, 147.7, 169.1.

5.1.36 7,8-Dihydronaphthalen-1-yl benzoate (138s)

The reaction was performed following the general procedure as in **5.1.22**, but using phenol **88j** (0.248 g, 1.70 mmol), BzCl (0.22 ml, 0.267 g, 1.90 mmol) and Et₃N (0.51 ml, 0.374 g, 3.70 mmol) in DCM (10 mL).⁷⁹ Purification by flash column chromatography (3-4% EtOAc in hexane) gave benzoyl protected alkene **138s** (0.398 g, 1.60 mmol, 94 %) as a white solid (MP: 58.1-58.7 °C).

7,8-dihydronaphthalen-1-yl benzoate (138s)

¹H NMR (300 MHz, CDCl₃) δ : 2.24-2.32 (m, 2H), 2.71 (t, J = 8.4 Hz, 2H), 6.04 (dt, J = 9.6, 4.5 Hz, 1H), 6.49 (dt, J = 9.6, 1.8 Hz, 1H), 6.96 (d, J = 7.5 Hz, 1H), 7.00 (dd, J = 8.1, 1.2 Hz, 1H), 7.17-7.22 (m, 1H), 7.48-7.54 (m, 2H), 7.61-7.66 (m, 1H), 8.21-8.25 (m, 2H).

¹³C NMR (75 MHz, CDCl₃) δ : 20.6 (CH₂), 22.3 (CH₂), 120.8 (CH), 123.8 (CH), 126.8 (CH), 127.2 (C), 127.3 (CH), 128.6 (CH), 129.0 (CH), 129.4 (C), 130.1 (CH), 133.5 (CH), 135.7 (C), 148.0 (C), 164.8 (C).

LRMS m/z (rel. int.): 250 (M^+ , 9), 144 (3), 128(11), 115 (10), 105 (100), 91 (2), 77 (36), 63 (3), 51 (10), 39 (2).

HRMS [ESI(+)] calcd. for $[C_{17}H_{14}O_2+Na]^+$ 273.0891, found 273.0890.

IR (film): 3035, 2935, 2887, 2834, 2127, 1735, 1651, 1601, 1583, 1569, 1491, 1451, 1395, 1342, 1314, 1296, 1266, 1247, 1229, 1212 cm^{-1} .

5.1.37 7-Methoxy-1,2-dihydronaphthalene (**1k**)

The reaction was performed following the general procedure **5.1.1**, but using ketone **85k** (2.000 g, 11.35 mmol), MeOH (80 mL) and $NaBH_4$ (0.4290 g, 11.35 mmol). After workup, solvent was removed under reduced pressure and alcohol **241** (1.986 g, 11.14 mmol, 98.0%) was obtained as white solid and used in the next step without purification.^{27,61}

The reaction was performed following the general procedure as in **5.1.1**, but using alcohol **241** (1.986 g, 11.14 mmol), toluene (60 mL) and $TsOH \cdot H_2O$ (cat. few crystals) at 130 °C. The crude product was purified by flash column chromatography (20-40% EtOAc in hexane) giving alkene **1k** (1.702 g, 10.6 mmol, 95%) as colorless oil.^{27,61}

7-Methoxy-1,2-dihydronaphthalene (**1k**)⁶¹

1H NMR (300 MHz, $CDCl_3$) δ : 2.24-2.31 (m, 2H), 2.76 (t, $J = 8.0$ Hz, 2H), 3.78 (s, 3H), 5.88 (dt, $J = 9.6, 4.4$ Hz, 1H), 6.40 (dt, $J = 9.6, 1.8$ Hz, 1H), 6.66-6.69 (m, 2H), 6.94 (d, $J = 9$ Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ : 22.9, 27.9, 55.1, 110.9, 113.7, 125.8, 126.7, 127.1, 127.3, 137.1, 158.5.

5.1.38 7,8-Dihydronaphthalen-2-ol (**88k**)

Under inert atmosphere N₂, NaH (6.24 g, 260 mmol, 60% in mineral oil) was washed with anhydrous hexanes (3 x 20 mL). After a few minutes, anhydrous DMF (75 mL) was added. To this mixture was slowly added a solution of EtSH (13.0 mL, 180 mmol, 30 equiv based on olefin **1k**) in anhydrous DMF (14 mL) at 0 °C and the resulting yellow solution was stirred for 20 min at rt. A solution of alkene **1k** (0.961 g, 6.0 mmol) in DMF (15 mL) was then added dropwise and the resulting mixture was stirred for 5 h at 140 °C. When the reaction becoming slightly brown, the mixture was cooled to the rt and a saturated solution of NH₄Cl was added. The mixture was extracted with Et₂O. The organic phase was washed with water, brine and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (20-40 % EtOAc in hexane) giving alkene **88k** (0.851 g, 5.8 mmol, 97%) as viscous liquid.⁸⁴

7,8-dihydronaphthalen-2-ol (**88k**)⁸⁴

¹H NMR (300 MHz, CDCl₃) δ: 2.23-2.31 (m, 2H), 2.74 (t, *J* = Hz, 8.4, 2H), 4.85 (s, 1H), 5.88 (dt, *J* = 9.6, 4.4 Hz, 1H), 6.40 (dt, *J* = 9.6, 1.8 Hz, 1H), 6.58-6.63 (m, 2H), 6.89 (d, *J* = 8.7 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ: 22.9, 27.8, 112.7, 114.8, 125.9, 127.0, 127.1, 127.4, 137.5, 154.4.

5.1.39 7,8-Dihydronaphthalen-2-yl acetate (**138k**)

The reaction was performed following the general procedure as in **5.1.22**, but using phenolic alkene **88k** (0.365 g, 2.50 mmol), DMAP (0.09 g, 0.07 mmol) and Ac₂O (0.9 mL, 9.5 mmol) in Et₃N (10 mL). Purification by flash column chromatography (3-5% EtOAc in hexane) gave acetyl protected alcohol **138k** (0.398 g, 2.11 mmol, 85%) as a colorless liquid.²⁷

7,8-Dihydronaphthalen-2-yl acetate (**138k**)⁸⁶

¹H NMR (300 MHz, CDCl₃) δ: 2.25-2.32 (m, 2H), 2.27 (s, 3H), 2.77 (t, *J* = 8.2 Hz, 2H), 5.96-6.02 (m, 1H), 6.43 (dt, *J* = 9.6, 1.8 Hz, 1H), 6.83-6.86 (m, 2H), 6.99 (d, *J* = 8.1 Hz, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ : 21.0, 22.7, 27.5, 119.1, 120.7, 126.5, 126.9, 128.3, 131.9, 136.9, 149.1, 169.6.

5.1.40 6-Methoxy-1,2-dihydronaphthalene (**1c**)

The reaction was performed following the general procedure **5.1.1**, but using ketone **85c** (0.705 g, 4.00 mmol), MeOH (40 mL) and NaBH_4 (0.152 g, 4.00 mmol). After workup, solvent was removed under reduced pressure and alcohol **242** (0.691 g, 3.88 mmol, 97%) was obtained as white solid and used in the next step without purification.

The reaction was performed following the general procedure as in **5.1.1**, but using alcohol **242** (0.691 g, 3.88 mmol), toluene (40 mL) and $\text{TsOH} \cdot \text{H}_2\text{O}$ (cat. few crystals) at 130 °C. After workup solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (1-2 % EtOAc in hexane) giving alkene **1c** (0.488 g, 3.04 mmol, 78%) as colorless oil.

6-Methoxy-1,2-dihydronaphthalene (**1c**)^{27,62}

^1H NMR (300 MHz, CDCl_3) δ : 2.25-2.33 (m, 2H), 2.72 (t, $J = 8.1$ Hz, 2H), 3.78 (s, 3H), 6.04 (dt, $J = 9.6, 4.4$ Hz, 1H), 6.42 (dt, $J = 9.6, 1.8$ Hz, 1H), 6.60 (d, $J = 2.7$, 1H), 6.67 (dd, $J = 8.1, 2.7$ Hz, 1H), 7.01 (d, $J = 8.4$ Hz, 1H)

^{13}C NMR (75 MHz, CDCl_3) δ : 23.5, 26.5, 55.1, 111.6, 111.7, 127.5, 127.7, 128.1, 129.2, 135.0, 158.2.

5.1.41 5,6-Dihydronaphthalen-2-ol (**88c**)

The reaction was performed following the general procedure as in **5.1.38**, but using alkene **1c** (0.481 g, 3.00 mmol), NaH (3.12 g, 130 mmol, 60% in mineral oil), EtSH (6.5 mL, 90

mmol, 30 equiv based on olefin **1c**) in DMF (35 mL) at 140 °C. The crude product was purified by flash column chromatography (10-15 % ethyl acetate in hexane) giving alkene **88c** (0.351 g, 2.40 mmol, 80%) as white solid. MP: 98-99 °C.

5,6-dihydronaphthalen-2-ol (**88c**)

¹H NMR (300 MHz, CDCl₃) δ: 2.25-2.32 (m, 2H), 2.71 (t, *J* = 8.1 Hz, 2H), 4.59 (s, 1H), 6.04 (dt, *J* = 9.6, 4.4 Hz, 1H), 6.38 (dt, *J* = 9.6, 1.8 Hz, 1H), 6.52 (d, *J* = 2.7 Hz, 1H), 6.59 (dd, *J* = 7.8, 2.7 Hz, 1H), 6.96 (d, *J* = 8.1, Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ: 23.5 (CH₂), 26.6 (CH₂), 112.9 (CH), 113.1 (CH), 127.5 (CH), 127.7 (C), 128.3 (CH), 129.5 (CH), 135.3 (C), 154.0 (C).

LRMS *m/z* (rel. int.): 146 (M⁺•, 100), 145 (71), 131 (45), 127 (43), 117 (36), 115 (55), 103 (5), 91 (12), 77 (7), 63 (14), 51 (13), 39 (10).

HRMS [ESI(+)] : calcd for [C₁₀H₁₀O+K]: 185,0369, found: 185,0361.

IR (film): 3247, 3027, 2936, 2880, 2851, 2818, 1629, 1614, 1574, 1492, 1477, 1465, 1435, 1426, 1395, 1349, 1327, 1282, 1265, 1215 cm⁻¹.

5.1.42 5,6-Dihydronaphthalen-2-yl acetate (**138c**)

The reaction was performed following the general procedure as in **5.1.22**, but using alkene **88c** (0.351 g, 2.40 mmol), DMAP (0.08 g, 0.065 mmol) and Ac₂O (0.9 ml, 9.0 mmol) in Et₃N (10 mL). Purification by flash column chromatography (3-5% EtOAc in hexane) gave acetyl protected alcohol **138c** (0.359 g, 1.90 mmol, 85%) as a colorless liquid.

5,6-Dihydronaphthalen-2-yl acetate (**138c**)

¹H NMR (300 MHz, CDCl₃) δ: 2.27-2.36 (m, 2H), 2.28 (s, 3H), 2.77 (t, *J* = 8.0 Hz, 2H), 6.06 (m, 1H), 6.41 (dt, *J* = 9.6, 1.8 Hz, 1H), 6.74 (d, *J* = 2.4 Hz, 1H), 6.81 (dd, *J* = 8.1, 2.4 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ: 21.1 (CH₃), 23.2 (CH₂), 26.8 (CH₂), 118.8 (CH), 119.4 (CH), 127.3 (CH), 128.2 (CH), 129.6 (CH), 132.9 (C), 135.3 (C), 149.2 (C), 169.7 (C).

LRMS m/z (rel. int.): 188 ($M^{+\bullet}$, 20), 146 (100), 145 (52), 131 (30), 127 (19), 117 (24), 115 (42), 91 (15), 77 (5), 63 (9), 43 (30), 39 (10).

HRMS [ESI(+)] : calcd for $[C_{12}H_{12}O_2+Na]$: 211,0735, found: 211,0724.

IR (film): 3034, 2935, 2885, 2831, 1761, 1609, 1575, 1491, 1432, 1369, 1328, 1271, 1210 cm^{-1} .

5.1.43 1-Methylene-1,2,3,4-tetrahydronaphthalene (**139**)

Under nitrogen atmosphere, t -BuOK (0.539 g, 4.80 mmol) was added to a stirred solution of Ph_3PMeBr (1.71 g, 4.8 mmol) (dried in BUCHI glass oven B-585 under vacuum for 5 hr) in anhydrous Et_2O (50 mL). The resulting canary yellow solution was stir for 1 h. A solution of the ketone **85a** (0.584 g, 4.00 mmol) in anhydrous Et_2O (5 mL) was added dropwise. After completion of the reaction the crude mixture was passed through a celite pad and washed with Et_2O (20 mL), concentrated under reduced pressure. The crude reaction mixture was then diluted with hexanes, and passed through a pad of silica gel by eluting with hexanes. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (1% EtOAc in hexane) giving alkene **139** (0.559 g, 3.87 mmol, 97%) as viscous liquid.⁸⁸

1-Methylene-1,2,3,4-tetrahydronaphthalene (**139**)⁸⁸

1H NMR (200 MHz, $CDCl_3$) δ : 1.80-1.93 (m, 2H), 2.50-2.60 (m, 2H), 2.83 (t, J = 6.4 Hz, 2H), 4.94 (d, J = 1.2 Hz, 1H), 5.46 (d, J = 0.8 Hz, 1H), 7.06-7.20 (m, 3H), 7.61-7.66 (m, 1H).

^{13}C NMR (50 MHz, $CDCl_3$) δ : 23.8, 30.4, 33.2, 107.8, 124.2, 125.8, 127.5, 129.2, 134.7, 137.3, 143.4.

5.2 Synthesis of chiral iodoarene compounds

5.2.1 (*R*)-Ethyl 2-(2-iodophenoxy)propanoate (**36m**)

To a stirred solution of 2-iodophenol (**144**) (5.15 g, 23.4 mmol), PPh₃ (9.19 g, 35.1 mmol) and (–) lactic acid ethyl ester (**35**) (3.99 mL, 35.1 mmol) in THF (50 mL) was added dropwise DIAD (6.91 mL, 35.1 mmol) at 0 °C. The reaction was allowed to warm to rt. After continues stirring for 6 h, the resulting mixture was concentrated under reduced pressure. Purification by silica gel flash column chromatography (2-3 % EtOAc in hexane) gave compound **36m** (6.88 g, 21.5 mmol, 92 %) as colorless oil $[\alpha]_D^{20} = -5.9$ ($c = 0.36$, CHCl₃).⁴⁹

(*R*)-Ethyl 2-(2-iodophenoxy)propanoate (**36m**)⁴⁹

¹H NMR (300 MHz, CDCl₃) δ : 1.24 (t, $J = 7.2$ Hz, 3H), 1.70 (d, $J = 6.9$ Hz, 3H), 4.23 (qd, $J = 7.2, 1.5$ Hz, 2H), 4.74 (q, $J = 6.9$ Hz, 1H), 6.73 (m, 2H), 7.25 (m, 1H), 7.78 (m, 1H).

¹³C NMR (75 MHz, CDCl₃) δ : 14.1, 18.5, 61.3, 74.1, 87.3, 113.4, 123.4, 129.3, 139.7, 156.6, 171.5.

5.2.2 (*R*)-2-(2-Iodophenoxy)propanoic acid (**36s**)

To a stirred solution of **36m** (4.00 g, 12.5 mmol) in THF (25.0 mL) and MeOH (25.0 mL) was added 2 mol/L NaOH (25.0 mL) and stirred overnight at rt. The reaction mixture was cooled to 0 °C, quenched with 1 mol/L HCl and extracted with EtOAc. The organic layers were dried over anhydrous MgSO₄ and the solvents were removed under reduced pressure gave acid **36s** (3.59 g, 12.3 mmol, 98%) as white solid. MP: 132.4-133 °C, $[\alpha]_D^{20} = 2.9$ ($c = 1.0$, THF), $[\alpha]_D^{26} = 2.43$ ($c = 1.0$, THF) (lit. $[\alpha]_D^{26} = 2.5$ ($c = 1.0$, THF)).⁴⁹

(*R*)-2-(2-Iodophenoxy)propanoic acid (**36s**)⁴⁹

^1H NMR (300 MHz, CDCl_3) δ : 1.74 (d, $J = 6.9$ Hz, 3H), 4.81 (q, $J = 6.9$ Hz, 1H), 6.778 (m, 2H), 7.28 (m, 1H), 7.80 (m, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ : 18.3, 73.6, 87.3, 113.4, 123.9, 129.5, 139.9, 155.9, 176.2.

5.2.3 (2*R*)-(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(2-iodophenoxy)propanoate (**36p**)

To a round bottomed flask were added acid **36s** (0.584 g, 2.00 mmol), (–)-menthol (**26**) (0.390 g, 2.5 mmol), DCC (0.515 g, 2.5 mmol) and DMAP (0.037 g, 0.300 mmol) in DCM (50 mL).⁹¹ The reaction mixture was stirred at rt for 6 h then filtered. The filtrate was extracted with aqueous NaHCO_3 solution. The organic layer was combined, dried over anhydrous MgSO_4 and filtered. The solvent was removed under the reduced pressure. Purification by silica gel flash column chromatography (3% EtOAc in hexane) gave compound **36p** in (0.805 g, 1.87 mmol, 94%) as white solid. MP: 53.5–54.6 °C (lit. 53–54 °C), $[\alpha]_D^{20} = -47.9$ ($c = 0.15$, CHCl_3).

(2*R*)-(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 2-(2-iodophenoxy)propanoate (**36p**)⁹²

^1H NMR (300 MHz, CDCl_3) δ : 0.52 (d, $J = 6.9$ Hz, 3 H), 0.73 (d, $J = 6.9$ Hz, 3H), 0.85 (m, 1H), 0.90 (d, $J = 6.3$ Hz, 3H), 1.01 (m, 3H), 1.33 (m, 2H), 1.60 (m, 2H), 1.70 (d, $J = 6.9$ Hz, 3H), 2.00 (m, 1H), 4.62 (td, $J = 10.8, 4.5$ Hz, 1H), 4.77 (q, $J = 6.6$ Hz, 1H), 6.71 (m, 2H), 7.23 (m, 1H), 7.78 (d, $J = 8.1, 1.5$ Hz, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ : 15.5, 18.5, 20.8, 22.0, 22.9, 25.5, 31.3, 34.1, 40.4, 46.7, 74.0, 75.5, 87.0, 112.7, 123.1, 129.2, 139.7, 156.5, 171.4.

5.2.4 (*R*)-2-(2-Iodophenoxy)-*N*-phenylpropanamide (**36q**)

The reaction was performed following the general procedure as in **5.2.3**, but using acid **36s** (0.584 g, 2.00 mmol), DCM (50 mL), aniline (**122a**) (0.233 g, 2.5 mmol), DCC (0.515 g, 2.5 mmol) and DMAP (0.037 g, 0.300 mmol).^{91,168} Purification by silica gel flash column chromatography (10 % EtOAc in hexane) gave compound **36q** in (0.589 g, 1.87 mmol, 80%) as white solid. MP: 128.6-129.3 °C, $[\alpha]_D^{20} = -99.3$ ($c = 0.17$, CHCl₃).

(R)-2-(2-Iodophenoxy)-N-phenylpropanamide (36q)

¹H NMR (300 MHz, CDCl₃) δ : 1.73 (d, $J = 6.6$ Hz, 3H), 4.91 (q, $J = 6.6$ Hz, 1H), 6.81 (td, $J = 7.5, 1.2$ Hz, 1H), 6.87 (dd, $J = 8.4, 1.2$ Hz, 1H), 7.11-7.17 (m, 1H), 7.31-7.38 (m, 3H), 7.63-7.67 (m, 2H), 7.82 (dd, $J = 7.8, 1.5$ Hz, 1H), 8.02 (bs, 1H).

¹³C NMR (75 MHz, CDCl₃) δ : 18.3 (CH₃), 75.9 (CH), 87.5 (C), 113.3 (CH), 119.8 (CH), 124.0 (CH), 124.7 (CH), 129.1 (CH), 129.9 (CH), 137.3 (C), 139.9 (CH), 155.0 (C), 169.1 (C).

HRMS [ESI(+)] : calcd. for [C₁₅H₁₄INO₂+H]⁺ 368.0147, found, 368.0149.

IR (film): 3248, 3134, 3059, 2981, 2918, 2850, 1669, 1598, 1582, 1570, 1544, 1498, 1470, 1439, 1376, 1287, 1277, 1246, 1204 cm⁻¹.

5.2.5 (R)-2-(2-Iodophenoxy)-N-(2,6-dimethylphenyl)propanamide (36r)

The reaction was performed following the general procedure **5.2.3**, but using acid **36s** (0.876 g, 3.00 mmol), dimethylaniline (**122b**) (0.462 mL, 3.75 mmol), DCC (0.768 g, 3.75 mmol) and DMAP (0.055 g, 0.45 mmol) in DCM (50 mL).^{91,168} Purification by silica gel flash column chromatography (5-20 % EtOAc in hexane) gave compound **36r** in (0.970 g, 2.45 mmol, 82 %) as white solid. MP: 171.8-173.2 °C, $[\alpha]_D^{20} = -52.7$ ($c = 0.16$, CHCl₃).

(R)-2-(2-Iodophenoxy)-N-(2,6-dimethylphenyl)propanamide (36r)

¹H NMR (300 MHz, CDCl₃) δ : 1.78 (d, $J = 6.6$ Hz, 3H), 2.19 (s, 6H), 4.99 (qd, $J = 6.6, 0.6$ Hz, 1H), 6.81 (dd, $J = 7.5, 1.6$ Hz, 1H), 6.92 (dd, $J = 8.7, 1.5$ Hz, 1H), 7.10 (m, 3H), 7.35 (ddd, $J = 8.2, 7.4, 1.6$ Hz, 1H), 7.83 (dd, $J = 7.8, 1.5$ Hz, 1H), 8.07 (bs, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ : 18.4 (CH_3), 18.7 (CH_3), 75.8 (CH), 87.3 (C), 113.2 (CH), 123.9 (CH), 127.5 (CH), 128.3 (CH), 129.8 (CH), 132.8 (C), 135.4 (C), 139.7 (CH), 155.1 (C), 169.6 (C).

HRMS [ESI(+)]: calcd. for $[\text{C}_{17}\text{H}_{18}\text{INO}_2+\text{H}]^+$ 396.0460, found, 396.0461.

IR (film): 3234, 3025, 2990, 2919, 1667, 1593, 1582, 1569, 1538, 1471, 1438, 1372, 1278, 1250, 1231 cm^{-1} .

5.2.6 (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-iodobenzoate (**36o**)

The reaction was performed following the general procedure **5.2.3**, but using iodo benzoic acid **36t** (0.496 g, 2.00 mmol), (-)-menthol (**26**) (0.390 g, 2.5 mmol), DCC (0.515 g, 2.5 mmol) and DMAP (0.037 g, 0.300 mmol) in DCM (50 mL).⁹¹ Purification by silica gel flash column chromatography (5 % EtOAc in hexane) gave compound **36o** in (0.741 g, 1.92 mmol, 96 %) as light yellow oil. $[\alpha]_{\text{D}}^{20} = -46.2$ ($c = 0.48$, CHCl_3), $[\alpha]_{\text{D}}^{20} = -45.4$ ($c = 0.48$, CHCl_3).¹⁶⁹

(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-iodobenzoate (**36o**)⁹³

^1H NMR (300 MHz, CDCl_3) δ : 0.82 (d, $J = 6.9$ Hz, 3H), 0.93 (t, $J = 9.9$ Hz, 7H), 1.14 (m, 2H), 1.54 (m, 2H), 1.73 (m, 2H), 2.01 (quind, $J = 6.9$, 2.7 Hz, 1H), 2.18 (m, 1H), 4.96 (td, $J = 10.8$, 4.5 Hz, 1H), 7.13 (ddd, $J = 7.8$, 7.2, 1.8 Hz, 1H), 7.39 (ddd, $J = 7.5$, 7.2, 1.2 Hz, 1H), 7.74 (ddd, $J = 7.8$, 1.5, 0.3 Hz, 1H), 7.98 (ddd, $J = 8.1$, 1.2, 0.3 Hz, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ : 16.2, 20.8, 22.0, 23.3, 26.3, 31.5, 34.2, 40.8, 47.1, 75.9, 93.8, 127.8, 130.4, 132.2, 136.0, 141.1, 166.2.

5.2.7 2-Iodobenzene-1,3-diol (**34**)

To a round bottomed flask were added resorcinol (**161**) (5.50 g, 50.0 mmol), H₂O (50 mL), I₂ (13.58 g, 53.5 mmol) and NaHCO₃ (4.49 g, 53.5 mmol). The reaction mixture was stirred at room temperature for 20 min. The excess iodine was quenched with aqueous solution of Na₂SO₃. The product was extracted with ether (3x30 mL) and was concentrated under reduced pressure. Purification by silica gel flash column chromatography (15-20 % EtOAc in hexane) gave compound **34** (8.36 g, 35.4 mmol, 71%) as white solid. MP: 98.5-100.8.⁹⁴

2-Iodobenzene-1,3-diol (**34**)⁹⁵

¹H NMR (200 MHz, acetone-d₆) δ : 6.46 (d, J = 8.0 Hz, 2H), 7.00 (t, J = 8 Hz, 1H), 8.89 (s, 2H).

¹H NMR (300 MHz, CDCl₃) δ : 5.28 (s, 2H), 6.55 (d, J = 8.1 Hz, 2H), 7.11 (t, J = 8.1 Hz, 1H)

¹³C NMR (75 MHz, CDCl₃) δ : 77.6, 107.3, 130.4, 155.6.

5.2.8 Diethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))((2*R*,2'*R*)-dipropionate ((*R,R*)-**36a**)

To a solution of 2-iodoresorcinol (**34**) (1.65 g, 15.0 mmol), PPh₃ (9.82 g, 37.5 mmol) and (–) lactic acid ethyl ester (**25**) (4.26 mL, 37.5 mmol) in THF (50 mL) was added dropwise DIAD (10.59 mL, 37.5 mmol) at 0 °C. The reaction was allowed to warm to rt. After continues stirring for 6 h, the resulting mixture was concentrated in *vacuo*. Purification by silica gel flash column chromatography (6-7 % EtOAc in hexane) gave compound **36a** (6.14 g, 14.1 mmol, 94%) as colorless oil. $[\alpha]_D^{20} = -21.8$ (c = 1.0, CHCl₃), (lit. $[\alpha]_D^{26} = -21.6$ (c = 1.0, CH₃Cl)).⁴⁹

Diethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))((2*R*,2'*R*)-dipropionate (**36a**)⁴⁹

¹H NMR (500 MHz, CDCl₃) δ : 1.24 (t, J = 7.2 Hz, 6H), 1.69 (d, J = 7.0 Hz, 6H), 4.21 (qd, J = 7.2, 1.2 Hz, 4H), 4.75 (q, J = 7.0 Hz, 2H), 6.38 (d, J = 8.5 Hz, 2H), 7.13 (t, J = 8.4 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃) δ : 14.1, 18.5, 61.2, 74.2, 80.7, 106.9, 129.4, 158.2, 171.6.

5.2.9 Diethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*S*,2'*S*)-dipropionate ((*S,S*)-**36a**)

The reaction was performed following the general procedure as in **5.2.9**, but using 2-iodoresorcinol (**34**) (0.66 g, 6.00 mmol), PPh₃ (3.98 g, 15.0 mmol) and (+) lactic acid ethyl ester (**35**) (1.46 mL, 13.0 mmol) and DIAD (4.24 mL, 15.0 mmol) in THF (20 mL). Purification by silica gel flash column chromatography (6-7 % EtOAc in hexane) gave compound **36a** (2.20 g, 5.04 mmol, 84%) as colorless oil. $[\alpha]_D^{20} = +21.2$ ($c = 1.0$, CHCl₃).

Diethyl 2,2'-((2-iodo-1,3-phenylene)bis(oxy))(2*R*,2'*R*)-dipropionate (**36a**)⁴⁹

¹H NMR (300 MHz, CDCl₃) δ : 1.24 (t, $J = 7.2$ Hz, 6H), 1.69 (d, $J = 6.9$ Hz, 6H), 4.21 (qd, $J = 7.2, 0.9$ Hz, 4H), 4.75 (q, $J = 6.9$ Hz, 2H), 6.38 (d, $J = 8.1$ Hz, 2H), 7.13 (t, $J = 8.4$ Hz, 1H),
¹³C NMR (75 MHz, CDCl₃) δ : 14.1, 18.5, 61.2, 74.2, 80.7, 106.9, 129.4, 158.3, 171.6.

5.2.10 (2*R*,2'*R*)-2,2'-((2-Iodo-1,3-phenylene)bis(oxy))dipropionic acid (**36b**)

The reaction was performed following the general procedure as in **5.2.2**, but using acid **36a** (5.40 g, 12.38 mmol), THF (40.0 mL), MeOH (40.0 mL) and 2 mol/L NaOH (40.0 mL). Purification by silica gel flash column chromatography (50 % EtOAc in hexane) gave compound **36b** (4.62 g, 12.2 mmol, 98%).⁴⁹ $[\alpha]_D^{26} = -6.3$ ($c = 1.0$, THF), (lit. $[\alpha]_D^{26} = -6.4$ ($c = 1.0$, THF)).⁴⁹

(2*R*,2'*R*)-2,2'-((2-Iodo-1,3-phenylene)bis(oxy))dipropionic acid (**36b**)⁴⁹

¹H NMR (200 MHz, DMSO-*d*₆) δ : 1.54 (d, $J = 6.8$ Hz, 6H), 4.85 (q, $J = 6.8$ Hz, 2H), 6.42 (d, $J = 8.4$ Hz, 2H), 7.21 (t, $J = 8.4$ Hz, 1H).
¹³C NMR (75 MHz, DMSO-*d*₆) δ : 18.3, 72.7, 79.5, 105.9, 129.6, 157.6, 172.6.

5.2.11 (2*R*,2'*R*)-2,2'-((2-Iodo-1,3-phenylene)bis(oxy))bis(N-mesitylpropanamide) (**36i**)

A stirred solution of carboxylic acid **36b** (2.00 g, 5.26 mmol) in SOCl_2 (20.0 mL) was refluxed for 1 h. To this mixture was added benzene (10 mL) and excess reagents were removed in *vacuo*. The residue was dissolved in DCM (20 mL) and was added with MsNH_2 (2.5 mL, 13.2 mmol) at 0 °C. The reaction was allowed to warm to rt for 14 h. The reaction mixture was treated with 1N HCl and extracted with DCM (3 x 15). The organic layers were dried over anhydrous MgSO_4 and the solvents were removed in *vacuo*. Purification by silica gel flash column chromatography (50 % EtOAc in hexane) gave compound **36i** in (2.91 g, 4.73 mmol, 90%) as white solid. $[\alpha]_D^{26} = -116.5$ (c 1.0, CHCl_3) (lit. $[\alpha]_D^{26} = -116.1$ (c 1.0, CHCl_3)).⁴⁹

(2*R*,2'*R*)-2,2'-((2-Iodo-1,3-phenylene)bis(oxy))bis(N-mesitylpropanamide) (**36i**)⁴⁹

^1H NMR (300 MHz, CDCl_3) δ : 1.78 (d, $J = 6.6$ Hz, 6H), 2.15 (s, 12 H), 2.27 (s, 6H), 5.01 (q, $J = 6.6$ Hz, 2H), 6.65 (d, $J = 8.4$ Hz, 2H), 6.90 (d, $J = 0.3$ Hz, 4H), 7.35 (t, $J = 8.4$ Hz), 8.00 (brs, 2H).

^{13}C NMR (75 MHz, CDCl_3) δ : 18.3, 18.8, 20.9, 76.1, 80.5, 107.1, 129.0, 130.1, 130.6, 135.1, 137.3, 157.0, 169.6.

5.3 Oxidation of cyclic alkenes mediated by HTIB

5.3.1 4-Methoxy-4*H*-chromene (174g) and *trans*-3,4-dimethoxy-3,4-dihydro-2*H*-chromene (175g)

To a stirred solution of 2*H*-chromene **1g** (0.135 g, 1.02 mmol) in MeOH (6 mL) was added HTIB (0.450 g, 1.15 mmol) at 0 °C. This mixture was stirred for 3 h. The reaction was

quenched with saturated solution of NaHCO_3 , extracted with EtOAc (3 x 10 mL), washed with brine (2 x 15 mL) and dried over anhydrous MgSO_4 . The crude product was purified by flash column chromatography (2-5% EtOAc in hexane) giving **174g** (0.106 g, 0.654 mmol, 66%) as colorless oil and **175g** (0.029 g, 0.15 mmol, 15%) as light yellowish oil.

4-Methoxy-4H-chromene (174g)

^1H NMR (200 MHz, CDCl_3) δ : 3.49 (s, 3 H), 5.58 (d, $J = 3.6$ Hz, 1 H), 5.86 (dd, $J = 9.6, 3.6$ Hz, 1 H), 6.73 (d, $J = 9.8$ Hz, 1 H), 6.91-7.01 (m, 2 H), 7.10-7.25 (m, 2 H).

^{13}C NMR (50 MHz, CDCl_3) δ : 55.0, 95.8, 116.5, 119.6, 120.7, 121.5, 126.6, 127.0, 129.3, 151.3.

LRMS m/z (rel. int.): 162 (M^+ , 23), 161 (21), 146 (4), 131 (100), 118 (5), 103 (11), 91 (15), 77 (21), 65 (8), 51 (13), 32 (20).

HRMS [ESI(+)] : calcd for $[\text{C}_{10}\text{H}_{10}\text{O}_2+\text{Na}]$: 185.0573, found: 185.0583.

IR (film): 3052, 2956, 2927, 2829, 1729, 1643, 1607, 1575, 1489, 1458, 1087, 1034 cm^{-1} .

***trans*-3,4-Dimethoxy-3,4-dihydro-2H-chromene (175g)**

^1H NMR (300 MHz, CDCl_3) δ : 3.46 (s, 3 H), 3.47 (s, 3 H), 3.66 (td, $J = 3.3, 1.8$ Hz, 1 H), 4.18 (dd, $J = 12, 1.8$ Hz, 1 H), 4.19 (dd, $J = 3.6, 1.5$ Hz, 1 H), 4.33 (ddd, $J = 11.7, 3.3, 1.5$ Hz, 1 H), 6.85- 6.89 (m, 1 H), 6.92 (dd, $J = 7.5, 1.2$ Hz, 1 H), 7.18-7.25 (m, 2 H).

^{13}C NMR (50 MHz, CDCl_3) δ : 56.5, 56.9, 62.8, 73.9 (2 C), 116.8, 119.4, 120.3, 129.8, 131.4, 154.1.

LRMS m/z (rel. int.): 194 (M^+ , 13), 162 (9), 136 (53), 121 (41), 107 (100), 91 (13), 77 (19), 65 (11), 51 (10).

HRMS [ESI(+)] : calcd for $[\text{C}_{11}\text{H}_{14}\text{O}_3+\text{Na}]$: 217.0835, found: 217.0832.

IR (film): 3074, 3042, 2983, 2931, 2892, 2825, 1698, 1609, 1585, 1489, 1463 cm^{-1} .

5.3.2 4-Methoxy-4*H*-chromene (**174g**) and *trans*-3,4-Dimethoxy-3,4-dihydro-2*H*-chromene (**175g**)

To a solution of 2*H*-chromene (**1g**) (0.126 g, 0.95 mmol) in MeOH (6 mL) at 0 °C was added drop wise BF₃·OEt₂ (0.126 mL, 1 mmol), followed by addition of HTIB (0.39 g, 1 mmol). Stirring was continued for 2.5 h at 0 °C. The reaction was quenched with a saturated solution of NaHCO₃ and extracted with EtOAc (3 x 10 mL), washed with brine (2 x 10 mL) dried over anhydrous MgSO₄. The solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel (2-5% EtOAc in hexanes) afforded 4-methoxy-4*H*-chromene (**174g**) (0.044 g, 0.29 mmol, 29%) as a colourless oil and *trans*-3,4-dihydro-3,4-dimethoxy-2*H*-chromene (**175g**) (0.044 g, 0.23 mmol, 23%) as light yellowish oil.

4-Methoxy-4*H*-chromene (**174g**)

¹H NMR (200 MHz, CDCl₃) δ: Data given above

¹³C NMR (50 MHz, CDCl₃) δ: Data given above

trans-3,4-Dimethoxy-3,4-dihydro-2*H*-chromene (**175g**)

¹H NMR (300 MHz, CDCl₃) δ: Data given above

¹³C NMR (50 MHz, CDCl₃) δ: Data given above

5.3.3 4-Methoxy-4*H*-chromene (**174g**) and *trans*-3,4-Dimethoxy-3,4-dihydro-2*H*-chromene (**175g**)

A magnetically stirred solution of 2*H*-chromene (**1g**) (0.135 g, 1.08 mmol) in TMOF (6 mL) maintained at 0 °C was treated with HTIB (0.446 g, 1.14 mmol). The resulting turbid solution was stirred and became clear after 30 min. Reaction mixture was stirred for another one

and half hour. After 2 h reaction was stop with the addition of saturated solution of NaHCO_3 , extracted with EtOAc (3 x 10 mL), washed with brine (2 x 15 mL) and dried over anhydrous MgSO_4 . The solvent was removed under reduced pressure. The resultant residue was purified by flash column chromatography (2-5% EtOAc in hexane) to afford the products 4-methoxy-4*H*-chromene (**174g**) (0.058g, 0.358 mmol, 36%) as a colourless oil and *trans*-3,4-dihydro-3,4-dimethoxy-2*H*-chromene (**175g**) (0.025 g, 0.13 mmol, 13%) as light yellowish oil.

4-Methoxy-4*H*-chromene (**174g**)

^1H NMR (200 MHz, CDCl_3) δ : Data given above

^{13}C NMR (50 MHz, CDCl_3) δ : Data given above

trans-3,4-Dihydro-3,4-dimethoxy-2*H*-chromene (**175g**)

^1H NMR (300 MHz, CDCl_3) δ : Data given above

^{13}C NMR (50 MHz, CDCl_3) δ : Data given above

5.3.4 4-Ethoxy-4*H*-chromene (**176g**) and *trans*-3,4-Diethoxy-3,4-dihydro-2*H*-chromene (**177g**)

HTIB (0.450 g, 1.14 mmol) was added at rt to a stirred solution of 2*H*-chromene (**1g**) (0.135 g, 1.02 mmol) in TEOF (6 mL). The resulting turbid solution became clear after 10 min. After 4 h, the reaction was quenched with saturated solution of NaHCO_3 . The mixture was extracted with EtOAc (3 x 10 mL), washed with brine solution (2 x 20 mL) and dried over anhydrous MgSO_4 . The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (3-5% EtOAc in hexane) giving 4*H*-chromene **176g** (0.075 g, 0.42 mmol, 42%) as a colorless oil and **177g** (0.018 g, 0.081 mmol, 8%) as a light yellowish oil.

4-Ethoxy-4*H*-chromene (**176g**)

^1H NMR (200 MHz, CDCl_3) δ : 1.20 (t, $J = 7$ Hz, 3 H), 3.65 (dq, $J = 9.7, 7$ Hz, 1 H), 3.94 (dq, $J = 9.7, 7$ Hz, 1 H), 5.68 (d, $J = 3.8$ Hz, 1 H), 5.85 (dd, $J = 9.6, 3.8$ Hz, 1 H), 6.71 (d, $J = 9.6$ Hz, 1 H), 6.96 (d, $J = 7.2$ Hz, 2 H), 7.10-7.24 (m, 2 H).

^{13}C NMR (50 MHz, CDCl_3) δ : 15.2, 63.4, 94.8, 116.5, 119.9, 120.7, 121.4, 126.5, 127.0, 129.2, 151.4.

LRMS m/z (rel. int.): 176 (M^+ , 42), 147 (35), 131 (100), 118 (5), 103 (25), 91 (36), 77 (32), 65 (18), 51 (23), 39 (22).

HRMS [ESI(+)] : calcd for $[\text{C}_{11}\text{H}_{12}\text{O}_2 + \text{Na}]$: 199.0725, found: 199.0715.

IR (film): 3046, 2976, 2927, 2880, 1718, 1644, 1607, 1576, 1497 cm^{-1} .

***trans*-3,4-Diethoxy-3,4-dihydro-2*H*-chromene (177g)**

^1H NMR (300 MHz, CDCl_3) δ : 1.20 (t, $J = 6.9$ Hz, 3 H), 1.24 (t, $J = 6.9$ Hz, 3 H), 3.59-3.69 (m, 2 H), 3.69-3.76 (m, 3 H), 4.20 (dd, $J = 11.7, 2.4$ Hz, 1 H), 4.23-4.29 (m, 2 H), 6.85 (dd, $J = 8.1, 1.2$ Hz, 1 H), 6.91 (td, $J = 7.5, 1.2$ Hz, 1 H), 7.19 (m, 1 H), 7.25 (dd, $J = 7.5, 1.5$ Hz, 1 H).

^{13}C NMR (75 MHz, CDCl_3) δ : 15.4, 15.6, 64.0, 64.7, 64.8, 73.0, 73.2, 116.7, 120.4, 120.5, 129.4, 131.0, 154.1.

LRMS m/z (rel. int.): 222 (M^+ , 6), 176 (9), 150 (42), 131 (16), 122 (71), 121 (100), 107 (30), 91 (28), 71 (26), 65 (13), 51 (10), 43 (22), 32 (29).

HRMS [ESI(+)] : calcd for $[\text{C}_{13}\text{H}_{18}\text{O}_3 + \text{Na}]$: 245.1148, found: 245.1152.

IR (film): 3042, 2976, 2926, 2882, 1624, 1610, 1586, 1489, 1464 cm^{-1} .

5.3.5 4-(2,2,2-Trifluoroethoxy)-4*H*-chromene (178g)

To a solution of 2*H*-chromene (**1g**) (0.142 g, 1.07 mmol) in TFE (6 mL) was added HTIB (0.462 g, 1.18 mmol) at 0 °C. Immediately after the addition of HTIB, the mixture became dark in color. After 2 h, the reaction was quenched with saturated solution of NaHCO_3 , extracted with EtOAc (3 x 10 mL), washed with brine solution (2 x 20 mL) and dried over

anhydrous MgSO_4 . The solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (2-3% EtOAc in hexanes) giving **178g** (0.590 g, 0.260 mmol, 24%) as colorless oil.

4-(2,2,2-Trifluoroethoxy)-4H-chromene (178g)

^1H NMR (300 MHz, CDCl_3) δ : 4.02 (dq, $J = 12.6, 3.9$ Hz, 1 H), 4.08 (dq, $J = 12.3, 3.9$ Hz, 1 H), 5.81 (d, $J = 3.9$ Hz, 1 H), 5.88 (dd, $J = 9.6, 3.6$ Hz, 1 H), 6.80 (d, $J = 9.3$ Hz, 1 H), 6.70-7.01 (m, 2 H), 7.14-7.17 (m, 1 H), 7.21-7.27 (m, 1 H).

^{13}C NMR (75 MHz, CDCl_3) δ : 64.0 (q, $J = 34.8$ Hz), 95.16, 116.5, 118.4, 120.3, 122.1, 123.7 (q, $J = 276$ Hz), 127.2, 127.6, 129.7, 150.6.

LRMS m/z (rel. int.): 230 (M^+ , 9), 131 (100), 118 (3), 102 (7), 91 (7), 77 (14).

HRMS [ESI(+)] : calcd for $[\text{C}_{11}\text{H}_9\text{F}_3\text{O}_2 + \text{Na}]$: 253.0452, found: 253.0459.

IR (film): 3048, 2927, 2855, 1644, 1610, 1584, 1489 cm^{-1} .

5.3.6 4-(2,2,2-Trifluoroethoxy)-4H-chromene (178g)

A well stirred mixture of 2H-chromene (**1g**) (0.132 g, 1 mmol) in TFE (6 mL) with $\text{BF}_3 \cdot \text{OEt}_2$ (0.135 mL, 1.1 mmol) at $0\text{ }^\circ\text{C}$ was added HTIB (0.431 g, 1.1 mmol). Reaction was stirred for 30 min. To this reaction mixture was added saturated solution of NaHCO_3 and was extracted with EtOAc (3 x 10 mL), washed with brine, dried over anhydrous MgSO_4 and concentrated under reduced pressure. The crude was purified by silica gel flash column chromatography (2-3% EtOAc in hexane) to obtain 4H-chromene **178g** (0.52 g, 0.23 mmol, 23%).

4-(2,2,2-Trifluoroethoxy)-4H-chromene (178g)

^1H NMR (300 MHz, CDCl_3) δ : Data given above

^{13}C NMR (75 MHz, CDCl_3) δ : Data given above

5.3.7 4-Methoxy-4*H*-thiochromene (183i)

The reaction was performed following the general protocol as in **5.3.1**, but using 2*H*-thiochromene (**1i**) (0.180 g, 1.25 mmol), MeOH (7 mL) and HTIB (0.52 g, 1.34 mmol) at rt. Purification by silica gel flash column chromatography (2-3% EtOAc in hexane) gave 4*H*-thiochromene **183i** (0.061g, 0.36 mmol, 29%) as yellowish oil.

4-Methoxy-4*H*-thiochromene (183i)

^1H NMR (200 MHz, CDCl_3) δ : 3.24 (s, 3H), 5.20 (d, $J = 6.2$ Hz, 1H), 6.13 (dd, $J = 10.2, 6.4$ Hz, 1H), 6.85 (d, $J = 10$ Hz, 1H), 7.13-7.36 (m, 4H).

^{13}C NMR (50 MHz, CDCl_3) δ : 53.2, 76.4, 119.3, 125.2, 127.1, 128.2, 129.1, 129.70, 129.71, 130.2.

LRMS m/z (rel. int.): 178 (M^+ , 19), 177 (9), 147 (100), 135 (17), 134 (17), 121 (3), 103 (7), 102 (8), 91 (17), 69 (11), 32 (85).

HRMS [ESI(+)] : calcd. for $[\text{C}_{10}\text{H}_{10}\text{OS}+\text{Na}]^+$ 201.0350, found 201.0348.

IR (film): 3060, 3031, 2975, 2892, 2873, 1920, 1720, 1685, 1635, 1626, 1581, 1471, 1430 cm^{-1} .

5.3.8 4-Methoxy-4*H*-thiochromene (183i)

The reaction was performed following the general protocol as in **5.3.3**, but using 2*H*-thiochromene (**1i**) (0.148 g, 1.0 mmol), TMOF (6 mL) and HTIB (0.43 g, 1.1 mmol). Purification by flash column chromatography (2-3% EtOAc in hexane) gave 4*H*-thiochromene **183i** (0.067g, 0.38 mmol, 38%) as yellowish oil.

4-Methoxy-4*H*-thiochromene (183i)

^1H NMR (200 MHz, CDCl_3) δ : Data given above

^{13}C NMR (50 MHz, CDCl_3) δ : Data given above

5.3.9 4-Ethoxy-4*H*-thiochromene (**184i**)

The reaction was performed following the general protocol as in **5.3.4**, but using 2*H*-thiochromene **1i** (0.120 g, 0.810 mmol), TEOF (5 mL) and HTIB (0.350 g, 0.891 mmol). Purification by flash column chromatography (2-3% EtOAc in hexane) gave **184i** (0.93 g, 0.48 mmol, 60%) as light yellow oil.

4-Ethoxy-4*H*-thiochromene (**184i**)

^1H NMR (200 MHz, CDCl_3) δ : 1.15 (t, J = 7.0 Hz, 3 H), 3.36 (dq, J = 9.1, 7.0 Hz, 1 H), 3.75 (dq, J = 9.1, 7.0 Hz, 1 H), 5.29 (d, J = 6.4 Hz, 1 H), 6.14 (dd, J = 10.2, 6.4 Hz, 1 H), 6.84 (d, J = 10.2 Hz, 1 H), 7.10-7.35 (m, 4 H).

^{13}C NMR (50 MHz, CDCl_3) δ : 14.8, 61.5, 75.0, 119.7, 125.2, 127.1, 128.2, 129.2, 129.7, 129.9, 130.1.

HRMS [ESI(+)] : calcd. for $[\text{C}_{11}\text{H}_{12}\text{OS}+\text{Na}]^+$ 215.0501, found, 215.0498.

Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{OS}$: C, 68.71; H, 6.29. Found: C, 68.65; H, 6.31.

IR (film): 3057, 3035, 2975, 2892, 2873, 1945, 1920, 1719, 1675, 1639, 1627, 1586, 1471, 1439 cm^{-1} .

5.3.10 *cis*-3,4-Dimethoxy-4-methyl-3,4-dihydro-2*H*-chromene (**185gg**)

The reaction was performed following the general protocol as in **5.3.1**, but using methylchromene **1gg** (0.202 g, 1.38 mmol), MeOH (8 mL) and HTIB (0.595 g, 1.51 mmol). Purification by flash column chromatography (2-5% EtOAc in hexane) gave **185gg** (0.183 g, 0.878 mmol, 64%) as colorless oil.

***cis*-3,4-Dimethoxy-4-methyl-3,4-dihydro-2*H*-chromene (185gg)**

^1H NMR (200 MHz, CDCl_3) δ : 1.56 (s, 3 H), 3.08 (s, 3 H), 3.50 (s, 3 H), 3.60 (dd, $J = 6.0, 2.8$ Hz, 1 H), 4.12 (dd, $J = 11.4, 6.0$ Hz, 1 H), 4.32 (dd, $J = 11.4, 2.6$ Hz, 1 H), 6.82 (dd, $J = 8.1, 1.3$ Hz, 1 H), 6.86-6.94 (m, 1 H), 7.12-7.21 (m, 1 H), 7.31 (dd, $J = 7.6, 1.7$ Hz, 1 H).

^{13}C NMR (50 MHz, CDCl_3) δ : 21.0, 49.8, 57.6, 62.8, 74.4, 76.1, 116.5, 120.1, 123.0, 127.8, 129.0, 154.1.

LRMS m/z (rel. int.): 208 ($\text{M}^+\bullet$, 3), 176 (13), 161 (13), 145 (49), 131 (79), 115 (52), 105 (49), 91 (34), 77 (48), 63 (44), 51 (53), 32 (100).

HRMS [ESI(+)] : calcd. for $[\text{C}_{12}\text{H}_{16}\text{O}_3 + \text{Na}]^+$ 231.0992, found 231.0995.

IR (film): 3069, 3036, 2981, 2938, 2896, 2826, 1628, 1608, 1582, 1488 cm^{-1} .

5.3.11 *cis*-3,4-Dihydro-3,4-dimethoxy-4-methyl-2*H*-chromene (185gg)

The reaction was performed following the general protocol as in **5.3.3**, but using 4-methyl-2*H*-chromene (**1gg**) (0.170 g, 1.164 mmol), TMOF (6 mL) and HTIB (0.50 g, 1.3 mmol). Purification by flash column chromatography (2-5% EtOAc in hexane) gave compound **185gg** (0.106g, 0.50 mmol, 44%) as colourless oil.

***cis*-3,4-Dihydro-3,4-dimethoxy-4-methyl-2*H*-chromene (185gg)**

^1H NMR (200 MHz, CDCl_3) δ : Data given above

^{13}C NMR (50 MHz, CDCl_3) δ : Data given above

5.3.12 *cis*-3,4-Diethoxy-4-methyl-3,4-dihydro-2*H*-chromene (186gg)

The reaction was performed following the general protocol as in **5.3.4**, but using methylchromene **1gg** (0.160 g, 1.109 mmol), TEOF (6 mL) and HTIB (0.478 g, 1.22 mmol). Purification by flash column chromatography (2-5% EtOAc in hexane) gave **186gg** (0.152 g, 0.643 mmol, 58%) as colorless oil.

***cis*-3,4-Diethoxy-4-methyl-3,4-dihydro-2*H*-chromene (186gg)**

^1H NMR (200 MHz, CDCl_3) δ : 1.10 (t, $J = 7$ Hz, 3 H), 1.22 (t, $J = 7$ Hz, 3 H), 1.59 (s, 3 H), 3.19-3.32 (m, 2 H), 3.67-3.81 (m, 3 H), 4.06 (dd, $J = 11.2, 7.0$ Hz, 1 H), 4.32 (dd, $J = 11.2, 3.2$ Hz, 1 H), 6.81 (dd, $J = 8.2, 1.2$ Hz, 1 H), 6.86-6.96 (m, 1 H), 7.17 (ddd, $J = 8.1, 7.2, 1.7$ Hz, 1 H), 7.34 (dd, $J = 7.8, 1.6$ Hz, 1 H).

^{13}C NMR (50 MHz, CDCl_3) δ : 15.5, 15.7, 22.4, 57.6, 64.4, 65.7, 74.2, 75.0, 116.5, 120.5, 124.5, 127.8, 129.0, 154.3.

LRMS m/z (rel. int.): 236 (M^+ , 4), 164 (45), 147 (14), 136 (35), 121 (100), 105 (7), 91 (12), 77 (9), 65 (9), 43 (21).

HRMS [ESI(+)]: calcd. for $[\text{C}_{14}\text{H}_{20}\text{O}_3 + \text{Na}]^+$ calcd for 259.1305, found: 259.1306.

IR (film): 3069, 3036, 2976, 2932, 2880, 1608, 1583, 1486, 1446 cm^{-1} .

5.3.13 4-(Bis(2,2,2-trifluoroethoxy)methyl)chromane(190b)

The reaction was performed following the general protocol as in **5.3.5**, but using dihydro-1-benzoxepine **87b** (0.146 g, 1.00 mmol, TFE (6 mL) and HTIB (0.43 g, 1.1 mmol). Purification by flash column chromatography (2-4% EtOAc in hexanes) gave **190b** (0.19 g, 0.55 mmol, 55%) as colorless oil.²⁷

4-(Bis(2,2,2-trifluoroethoxy)methyl)chromane (190b)

^1H NMR (300 MHz, CDCl_3) δ : 2.00-2.2 (m, 2 H), 3.06-3.11 (m, 1 H), 3.78-4.01 (m, 4 H), 4.10-4.26 (m, 2 H), 4.85 (d, $J = 7.2$ Hz, 1 H), 6.81-6.84 (m, 1 H), 6.89 (dd, $J = 7.5, 1.2$ Hz, 1 H), 7.13-7.18 (m, 1 H), 7.26 (dd, $J = 7.8, 1.5$ Hz, 1 H).

^{13}C NMR (75 MHz, CDCl_3) δ : 22.7, 36.6, 62.6 (q, $J = 139.5$ Hz, OCH_2CF_3), 63.1, 64.8 (q, $J = 138.6$ Hz, OCH_2CF_3), 105.8, 117.2, 119.0, 120.3, 123.1 (q, $J = 1105.8$ Hz, OCH_2CF_3), 123.6 (q, $J = 1104.6$ Hz, OCH_2CF_3), 128.7, 130.8, 155.0.

LRMS m/z (rel. int.): 344 ($\text{M}^+\bullet$, 7), 245 (6), 211 (76), 145 (18), 133 (100), 115 (13), 105 (73), 83 (63), 77 (44), 51 (25), 39 (14).

HRMS [ESI(+)] : calcd. for $[\text{C}_{14}\text{H}_{14}\text{F}_6\text{O}_3 + \text{Na}]^+$ 367.0739, found 367.0753.

IR (film): 3073, 3040, 2948, 2899, 1716, 1622, 1608, 1582, 1569, 1491, 1454 cm^{-1} .

5.3.14 4-(Dimethoxymethyl)chromane (194b)

The reaction was performed following the general protocol as in **5.3.1**, but using alkene **87b** (0.073 g, 0.50 mmol), MeOH/HTIB (4:1) (10 mL) and HTIB (0.294 g, 0.750 mmol) at 0 °C for 5 hours. The crude product was purified by flash column chromatography (5-10 % EtOAc in hexane) giving acetal **194b** (0.053 g, 0.255 mmol, 51%) as colourless oil and starting material **87b** (0.015 g, 0.103 mmol, 20%).²⁷

4-(Dimethoxymethyl)chromane (194b)

^1H NMR (300 MHz, CDCl_3) δ : 1.92-2.04 (m, 1H), 2.10-2.18 (m, 1H), 3.00-3.06 (m, 1H), 3.35 (s, 3H), 3.40 (s, 3H), 4.17-4.21 (m, 2H), 4.45 (d, $J = 6.3$ Hz, 1H), 6.79-6.88 (m, 2H), 6.10-6.15 (m, 1H), 7.29 (dddd, $J = 7.8, 1.8, 0.9, 0.3$ Hz, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ : 23.0 (CH_2), 36.5 (CH), 53.9 (CH_3), 55.7 (CH_3), 63.8 (CH_2), 107.6 (CH), 116.8 (CH), 119.9 (CH), 121.2 (C), 127.8 (CH), 130.7 (CH), 155.0 (C).

LRMS m/z (rel. int.): 208 ($\text{M}^+\bullet$, 2), 177 (3), 145 (7), 133 (6), 115 (4), 105 (9), 91 (3), 77 (9), 75 (100), 65 (2), 63 (3), 47 (20), 39 (4).

Anal. Calcd for $\text{C}_{12}\text{H}_{16}\text{O}_3$: C, 69.21; H, 7.74. Found: C, 68.94; H, 7.77.

IR (film): 3067, 3036, 2931, 2832, 1607, 1581, 1490, 1453, 1373, 1308, 1270, 1253, 1226 cm^{-1} .

5.3.15 (3,4-Dihydro-2H-chromen-4-yl)methanol (**191b**) and chroman-4-ylmethylene bis(4-methylbenzenesulfonate) (**192b**)

A mixture of **87b** (0.155 g, 1.06 mmol) at 0 °C was stirred with HTIB (0.431 g, 1.10 mmol) for 5 min in HFIP/DCM (1:4) (6 mL) and H₂O (0.4 mL, 22 equiv) (TLC monitoring). After the starting material was consumed, NaBH₄ (5 equiv) was added. This mixture was stirred for 2 h at rt. When the reaction was complete, H₂O was added and the mixture was extracted with EtOAc, washed with brine and dried over anhydrous MgSO₄. The solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (2–15%, EtOAc in hexane) giving alcohol **191b** (0.152 g, 0.930 mmol, 87%) and **192b** (0.46 g, 0.10 mmol, 9%).²⁷

(3,4-Dihydro-2H-chromen-4-yl)methanol (**191b**)

¹H NMR (300 MHz, CDCl₃) δ: 1.70 (s, 1 H), 2.04–2.11 (m, 2 H), 2.95–3.03 (m, 1 H), 3.80 (dd, *J* = 11.0, 8.0 Hz, 1 H), 3.89 (dd, *J* = 10.8, 5.1 Hz, 1 H), 4.17–4.21 (m, 2 H), 6.83 (dd, *J* = 8.1, 1.2 Hz, 1 H), 6.87 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.09–7.18 (m, 2 H).

¹³C NMR (75 MHz, CDCl₃) δ: 24.4, 36.0, 63.3, 66.4, 117.1, 120.3, 122.0, 127.9, 129.1, 155.2.

LRMS *m/z* (rel. int.): 164 (M⁺, 30), 133 (100), 131 (15), 105 (66), 103 (21), 77 (34), 63 (6), 51 (16), 39 (20).

HRMS [ESI(+)] : calcd. for [C₁₀H₁₂O₂+Na]⁺ 187.0735, found 187.0741.

IR (film): 3437, 3071, 3036, 2928, 2878, 1607, 1580, 1490, 1453 cm⁻¹.

Chroman-4-ylmethylene bis(4-methylbenzenesulfonate) (**192b**)

¹H NMR (300 MHz, CDCl₃) δ: 1.97–2.09 (m, 1 H), 2.21–2.30 (m, 1 H), 2.40 (s, 3 H), 2.45 (s, 3 H), 3.25–3.29 (m, 1 H), 4.01–4.13 (m, 2 H), 6.59 (d, *J* = 4.5 Hz, 1 H), 6.66–6.71 (m, 2 H), 6.95 (ddd, *J* = 8.1, 1.5, 0.9 Hz, 1 H), 7.05–7.11 (m, 1 H), 7.12–7.16 (m, 2 H), 7.28–7.33 (m, 2 H),

7.40 (t, $J = 1.8$ Hz, 1 H), 7.42 (t, $J = 1.8$ Hz, 1 H), 7.75 (t, $J = 1.8$ Hz, 1 H), 7.77 (t, $J = 1.8$ Hz, 1 H).

^{13}C NMR (75 MHz, CDCl_3) δ : 21.2, 21.6, 21.7, 38.5, 63.5, 100.3, 109.7, 117.1, 117.3, 120.4, 127.7 (2 C), 128.1 (2 C), 128.6, 129.6 (2 C), 129.8 (2 C), 132.7, 133.0, 145.1, 145.4, 155.3.

HRMS [ESI(+)]: calcd. for $[\text{C}_{24}\text{H}_{24}\text{O}_7\text{S}_2+\text{Na}]^+$ 511.0856, found 511.0858.

IR (film): 3066, 3040, 2975, 2929, 2591, 1935, 1914, 1597, 1584, 1492 cm^{-1} .

5.3.16 Chroman-4-ylmethylene bis(4-methylbenzenesulfonate) (**192b**)

A stirred mixture of HFIP/DCM (1:4) (6 mL) as a solvent was charged with benzoxepine **87b** (0.156 g, 1.07 mmol). HTIB (0.431 g, 1.10 mmol) was added to reaction mixture at 0 °C. After 5 min the starting material was finished (monitored by TLC), the reaction mixture was added NaBH_4 in excess (5 equiv.). The reaction was allowed to reach rt. After 2.5 h reaction was quenched with H_2O , extracted (EtOAc), washed with brine, dried over anhydrous MgSO_4 . The solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (2-12% EtOAc in hexane), gave acetal **192b** (0.176 g, 0.360 mmol, 34 %) and impure aldehyde **193b** (0.26 g, 0.16 mmol, 15%) as colorless oil.²⁷

Chroman-4-ylmethylene bis(4-methylbenzenesulfonate) (**192b**)

^1H NMR (300 MHz, CDCl_3) δ : given above

^{13}C NMR (75 MHz, CDCl_3) δ : given above

5.3.17 1-(3,4-Dihydro-2H-chromen-4-yl)ethanone (**195bb**)

The reaction was performed following the general protocol as in **5.3.5**, but using methylbenzoxepine **87bb** (0.135 g, 0.843 mmol), HTIB (0.363 g, 0.930 mmol) and TFE (6 mL). Purification by flash column chromatography (10% EtOAc in hexanes) gave **195bb** in (0.86 g, 0.49 mmol, 58%) as colorless oil.²⁷

1-(3,4-Dihydro-2H-chromen-4-yl)ethanone (195bb)

¹H NMR (300 MHz, CDCl₃) δ : 2.05-2.15 (m, 1 H), 2.20 (d, J = 0.3 Hz, 3 H), 2.22-2.32 (m, 1 H), 3.80 (t, J = 6 Hz, 1 H), 4.12-4.24 (m, 2 H), 6.84-6.87 (m, 1 H), 6.90 (dd, J = 7.5, 1.5 Hz, 1 H), 7.06 (dddd, J = 7.5, 1.5, 0.9, 0.3 Hz, 1 H), 7.14-7.20 (m, 1 H).

¹³C NMR (75 MHz, CDCl₃) δ : 24.5, 28.0, 48.5, 63.8, 117.4, 119.0, 120.5, 128.7, 130.0, 154.7, 208.8.

LRMS m/z (rel. int.): 176 (M⁺•, 58), 148 (9), 133 (42), 120 (100), 105 (8), 91 (94), 77 (23), 65 (18), 51 (19), 39 (34).

HRMS [ESI(+)] : calcd. for [C₁₁H₁₂O₂+Na]⁺ 199.073, found 199.0743.

IR (film): 3067, 3070, 2967, 2930, 2885, 1708, 1607, 1581, 1490, 1453 cm⁻¹.

5.3.18 (2,2-Dimethyl-2,3-dihydrobenzofuran-3-yl)methanol (200h)

The reaction was performed following the general protocol as in **5.3.15**, but using dimethylchromene **1h** (0.192 g, 1.20 mmol), HTIB (0.517g, 1.32 mmol), HFIP/DCM (1:4) (6 mL) and H₂O (22 equiv) at 0 °C. NaBH₄ was added in excess (5 equiv). Purification by flash column chromatography (15% EtOAc in hexane) gave alcohol **200h** (0.66 g, 0.37 mmol, 31%) as colorless oil.²⁷

(2,2-Dimethyl-2,3-dihydrobenzofuran-3-yl)methanol (200h)

¹H NMR (200 MHz, CDCl₃) δ : 1.47 (s, 3 H), 1.48 (s, 3 H), 1.84 (s, 1 H), 3.21 (t, J = 6.6 Hz, 1 H), 3.87 (d, J = 6.8 Hz, 2 H), 6.75 (d, J = 7.8 Hz, 1 H), 6.84 (td, J = 7.4, 0.8 Hz, 1 H), 7.10-7.25 (m, 2 H).

^{13}C NMR (75 MHz, CDCl_3) δ : 22.0, 29.3, 53.0, 62.6, 88.4, 109.8, 120.0, 124.8, 128.1, 128.7, 158.5.

LRMS m/z (rel. int.): 178 (M^+ , 33), 147 (100), 131 (17), 119 (47), 107 (13), 91 (49), 77 (18), 65 (7), 51 (8), 39 (14).

HRMS [ESI(+)]: calcd. for $[\text{C}_{11}\text{H}_{14}\text{O}_2+\text{Na}]^+$ 201.0886, found 201.0879.

IR (film): 3452, 2973, 2930, 2874, 1611, 1596, 1482, 1461 cm^{-1} .

5.3.19 3-(Dimethoxymethyl)-2,2-dimethyl-2,3-dihydrobenzofuran (201h)

The reaction was performed following the general protocol as in **5.3.1**, but using dimethylchromene **1h** (0.142 g, 0.890 mmol), HTIB (0.382 g, 0.980 mmol) and MeOH (6 mL). Purification by flash column chromatography (2-5% EtOAc in hexanes) gave **201h** (0.60 g, 0.27 mmol, 30%) as colorless oil.

3-(Dimethoxymethyl)-2,2-dimethyl-2,3-dihydrobenzofuran (201h)

^1H NMR (300 MHz, CDCl_3) δ : 1.35 (s, 3 H), 1.55 (s, 3 H), 3.41 (s, 3 H), 3.43 (s, 3 H), 3.44 (d, J = 5.1 Hz, 1 H), 4.52 (d, J = 5.1 Hz, 1 H), 6.72 (dt, J = 4.8, 0.3 Hz, 1 H), 6.83 (td, J = 4.5, 0.6 Hz, 1 H), 7.11-7.15 (m, 1 H), 7.34 (dtd, J = 4.5, 0.9, 0.3 Hz, 1 H).

^{13}C NMR (75 MHz, CDCl_3) δ : 22.2, 29.0, 52.2, 52.3, 53.8, 88.3, 103.9, 109.5, 120.1, 126.3, 126.6, 128.5, 158.7.

LRMS m/z (rel. int.): 222 (M^+ , 2), 159 (8), 131 (4), 91 (5), 75 (100), 45 (7).

HRMS [ESI(+)]: calcd. for $[\text{C}_{13}\text{H}_{18}\text{O}_3+\text{Na}]^+$ 245.1148, found 245.1140.

IR (film): 3045, 2974, 2934, 2831, 1610, 1594, 1478, 1460 cm^{-1} .

5.3.20 1-(2,2-Dimethyl-2,3-dihydrobenzofuran-3-yl)ethanone (**202hh**)

The reaction was performed following the general protocol as in **5.3.1**, but using trimethylchromene **1hh** (0.120 g, 0.690 mmol), HTIB (0.297 g, 0.760 mmol) and MeOH (5 mL). Purification by flash column chromatography (2-4% EtOAc in hexane) gave **202hh** in (0.031 g, 0.16 mmol, 24%) as colorless oil.

1-(2,2-Dimethyl-2,3-dihydrobenzofuran-3-yl)ethanone (**202h**)

^1H NMR (200 MHz, CDCl_3) δ : 1.43 (s, 3 H), 1.52 (s, 3 H), 2.05 (s, 3 H), 3.88 (s, 1 H), 6.83 (d, J = 8 Hz, 1 H), 6.91 (dd, J = 7.4, 1 Hz, 1 H), 7.14 (d, J = 7.4 Hz, 1 H), 7.18-7.27 (m, 1 H).

^{13}C NMR (50 MHz, CDCl_3) δ : 23.3, 29.4, 65.4, 88.4, 11.4, 120.8, 125.9, 126.1, 129.5, 159.2, 207.4.

LRMS m/z (rel. int.): 190 (M^+ , 15), 147 (100), 131 (20), 119 (55), 103 (7), 91 (50), 77 (18), 63 (6), 51 (10), 43 (61).

HRMS [ESI(+)] : calcd. for $[\text{C}_{12}\text{H}_{14}\text{O}_2 + \text{Na}]^+$ 213.0886, found 213.0877.

IR (film): 3050, 2979, 2934, 2873, 1704, 1610, 1596, 1480, 1460 cm^{-1} .

5.3.21 1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1H-indene (**16a**)

To a solution of alkene **1a** (0.390 g, 3.00 mmol) in TFE (45 mL) was added HTIB (1.41 g, 3.60 mmol) at 0 °C. Immediately after the addition of HTIB color of reaction mixture became dark. The reaction mixture was stirred at 0 °C for 5 min. The reaction was quenched with a saturated solution of NaHCO_3 . The reaction mixture was extracted with EtOAc (3 x 15 mL), washed with brine (2 x 10 mL) and dried over anhydrous MgSO_4 . The solvent was evaporated

under reduced pressure. The crude product was purified by flash column chromatography (2% EtOAc in hexanes) giving acetal **16a** (0.710 g, 2.16 mmol, 72%) as colorless oil.²⁷

1-(bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1H-indene (16a)²⁷

¹H NMR (300 MHz, CDCl₃) δ : 1.96-2.08 (m, 1H), 2.19-2.31 (m, 1H), 2.83-3.03 (m, 2H), 3.47 (q, J = 9.0 Hz, 1H), 3.86-4.05 (m, 4H), 4.70 (d, J = 8.1 Hz, 1H), 7.15-7.24 (m, 3H), 7.38-7.41 (m, 1H).

¹³C NMR (75 MHz, CDCl₃) δ : 27.1, 31.1, 47.1, 61.8 (q, J = 34.8 Hz), 63.3 (q, J = 34.8 Hz), 105.3, 123.7 (q, J = 276.07 Hz), 123.8 (q, J = 276.0 Hz), 124.6, 125.4, 126.4, 127.5, 140.7, 144.5.

5.3.22 *N*-(1-(Dimethoxymethyl)-2,3-dihydro-1H-inden-5-yl)acetamide (**7l**)

To a solution of alkene **1l** (0.094 g, 0.50 mmol) in MeOH (10 mL) was added HTIB (0.235 g, 0.60 mmol) at 0 °C for 10 min. The reaction was quenched with a saturated solution of NaHCO₃. The reaction mixture was extracted with EtOAc (3 x 15 mL), washed with brine (2 x 10 mL) and dried over anhydrous MgSO₄. The solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (40-50 % EtOAc in hexane), giving acetal **7l** (0.084 g, 0.34 mmol, 67%) as light yellowish solid. MP: 68.2-69 °C (lit. 68.4-69.3 °C).²⁷

N-(1-(dimethoxymethyl)-2,3-dihydro-1H-inden-5-yl)acetamide (**7l**)²⁷

¹H NMR (300 MHz, CDCl₃) δ : 1.93-2.02 (m, 1H), 2.15 (s, 3H), 2.17-2.23 (m, 1H), 2.77-2.97 (m, 2H), 3.37 (s, 3H), 3.39 (m, 1H), 3.42 (s, 3H), 4.27 (d, J = 7.5 Hz, 1H), 7.14 (dd, J = 8.4, 1.8 Hz, 1H), 7.31 (bs, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.46 (s, 1H).

¹³C NMR (75 MHz, CDCl₃) δ : 24.5, 27.5, 31.4, 47.0, 52.9, 54.2, 107.2, 116.3, 118.1, 125.7, 136.7, 138.9, 145.8, 168.3.

5.3.23 Reaction of *N*-(7,8-dihydronaphthalen-2-yl)-4-methylbenzenesulfonamide (**1n**) with HTIB

The reaction was performed following the general protocol as in **5.3.22**, but using alkene **1n** (0.150 g, 0.50 mmol), HTIB (0.235 g, 0.60 mmol) and MeOH (10 mL) at 0 °C.²⁷ The crude product was purified by flash column chromatography (20-50 % EtOAc in hexane) giving *trans*-**8n** (0.019 g, 0.052 mmol, 10%) as viscous colorless oil, *cis*-**8n** (0.068 g, 0.19 mmol, 37%) as viscous colorless oil and starting material **1n** (0.021 g, 0.070 mmol, 14%) was recovered.

N-((5*R*,6*R*)-5,6-Dimethoxy-5,6,7,8-tetrahydronaphthalen-2-yl)-4-methylbenzenesulfonamide (*trans*-**8n**)

¹H NMR (300 MHz, CDCl₃) δ: 1.82-1.92 (m, 1H), 1.99-2.09 (m, 1H), 2.37 (s, 3H), 2.57-2.80 (m, 2H), 3.42 (s, 3H), 3.48 (s, 3H), 3.65-3.70 (m, 1H), 4.14 (d, *J* = 4.8 Hz, 1H), 6.82-6.88 (m, 3H), 7.17-7.23 (m, 3H), 7.67 (d, *J* = 8.7 Hz, 2H).

¹³C NMR (75 MHz, CDCl₃) δ: 21.5 (CH₃), 22.9 (CH₂), 25.1 (CH₂), 56.5 (CH₃), 57.6 (CH₃), 77.5 (CH), 79.1 (CH), 118.5 (CH), 120.5 (CH), 127.2 (CH), 129.6 (CH), 130.9 (CH), 131.4 (C), 135.9 (C), 136.2 (C), 138.2 (C), 143.7 (C).

HRMS [ESI(+)] : calcd. for [C₁₉H₂₃NO₄S+K]⁺ 400.0985, found 400.0988.

IR (film): 3257, 2932, 2825, 1919, 1614, 1599, 1502, 1463, 1399, 1341, 1320, 1292, 1270, 1185, 1162 cm⁻¹.

N-((5*R*,6*S*)-5,6-Dimethoxy-5,6,7,8-tetrahydronaphthalen-2-yl)-4-methylbenzenesulfonamide (*cis*-**8n**)

¹H NMR (300 MHz, CDCl₃) δ: 1.82-1.90 (m, 1H), 2.08-2.18 (m, 1H), 2.36 (s, 1H), 2.60-2.71 (m, 1H), 2.84-2.91 (m, 1H), 3.42 (s, 3H), 3.44 (s, 3H), 3.59 (dt, *J* = 9.9, 3.0 Hz, 1H), 4.26 (d, *J* = 2.7 Hz, 1H), 6.86 (d, *J* = 2.1 Hz, 1H), 6.90 (dd, *J* = 8.1, 2.4, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.21 (dd, *J* = 8.7, 0.6 Hz, 2H), 7.50 (bs, 1H), 7.69 (dt, *J* = 8.4, 1.8 Hz, 2H).

^{13}C NMR (75 MHz, CDCl_3) δ : 21.4 (CH_3), 22.1 (CH_2), 26.8 (CH_2), 56.3 (CH_3), 57.0 (CH_3), 77.3 (CH), 77.5 (CH), 117.9 (CH), 120.6 (CH), 127.1 (CH), 129.5 (CH), 130.5 (CH), 131.1 (C), 136.1 (C), 136.4 (C), 137.7 (C), 143.7 (C).

HRMS [ESI(+)] calcd. for $[\text{C}_{19}\text{H}_{23}\text{NO}_4\text{S}+\text{Na}]^+$ 384.1245, found 384.1248.

IR (film): 3249, 3065, 2932, 2827, 1919, 1674, 1647, 1612, 1500, 1463, 1399, 1340, 1320, 1292, 1230 cm^{-1} .

N-(7,8-Dihydronaphthalen-2-yl)-4-methylbenzenesulfonamide (**1n**)

^1H NMR (300 MHz, CDCl_3) δ : Data given above

^{13}C NMR (75 MHz, CDCl_3) δ : Data given above

5.3.24 1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1*H*-inden-4-yl acetate (**16j**)

The reaction was performed following the general protocol as in **5.3.21**, but using alkene **138j** (0.094 g, 0.50 mmol), HTIB (0.235 g, 0.60 mmol) and TFE (10 mL) at 0 °C for 5 min.²⁷ The crude product was purified by flash column chromatography (4-5 % EtOAc in hexane) giving acetal **16j** (0.128 g, 0.33 mmol, 66%) as white solid (MP: 61.6-63.4 °C).

1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1*H*-inden-4-yl acetate (**16j**)

^1H NMR (300 MHz, CDCl_3) δ : 1.98-2.10 (m, 1H), 2.22-2.32 (m, 1H), 2.30 (s, 3H), 2.70-2.91 (m, 2H), 3.47-3.55 (m, J = Hz, 1H), 3.84-4.07 (m, 4H), 4.71 (d, J = 8.1 Hz, 1H), 6.94 (dt, J = 7.8 Hz, 1H), 7.21 (t, J = 7.8 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ : 20.8 (CH_3), 26.8 (CH_2), 28.1 (CH_2), 47.5 (CH), 61.8 (q, J = 34.8 Hz) (CH_2), 63.3 (q, J = 34.8 Hz) (CH_2), 105.0 (CH), 120.6 (CH), 123.2 (CH), 123.6 (q, J = 276 Hz) (CF_3), 123.7 (q, J = 276 Hz) (CF_3), 128.0 (CH), 136.6 (C), 143.3 (C), 147.1 (C), 168.9 (C).

HRMS [ESI(+)] calcd. for $[\text{C}_{16}\text{H}_{16}\text{F}_6\text{O}_4+\text{Na}]^+$ 409.0850, found 409.0851.

IR (film): 2947, 1764, 1615, 1587, 1468, 1433, 1372, 1281, 1213 cm^{-1} .

5.3.25 1-(bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1H-inden-5-yl acetate (**16k**)

The reaction was performed following the general protocol as in **5.3.21**, but using alkene **138k** (0.094 g, 0.50 mmol), HTIB (0.235 g, 0.60 mmol) and TFE (10 mL) at 0 °C for 5 min.²⁷ The crude product was purified by flash column chromatography (4-5 % ethyl acetate in hexane) giving acetal **16k** (0.117 g, 0.30 mmol, 60%) as viscous colorless liquid.

1-(bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1H-inden-5-yl acetate (**16k**)

¹H NMR (300 MHz, CDCl₃) δ: 1.97-2.09 (m, 1H), 2.21-2.33 (m, 1H), 2.28 (s, 3H), 2.82-3.01 (m, 2H), 3.43 (q, *J* = 7.8 Hz, 1H), 3.86-4.08 (m, 4H), 4.68 (d, *J* = 8.4 Hz, 1H), 6.87 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.94 (s, 1H), 7.38 (d, *J* = 8.1 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ: 21.0 (CH₃), 27.4 (CH₂), 31.1 (CH₂), 46.4 (CH), 61.6 (q, *J* = 34.8 Hz) (CH₂), 63.3 (q, *J* = 34.8 Hz) (CH₂), 105.1 (CH), 117.8 (CH), 119.7 (CH), 123.6 (q, *J* = 276 Hz) (CF₃), 123.7 (q, *J* = 276 Hz) (CF₃), 126.1 (CH), 138.3 (C), 146.1 (C), 150.3 (C), 169.7 (C).

LRMS *m/z* (rel. int.): 386 (M⁺•, 4), 344 (7), 245 (7), 211 (14), 175 (8), 145 (6), 133 (100), 115 (7), 105 (11), 83 (11), 77 (6), 43 (19).

HRMS [ESI(+)]: calcd. for [C₁₆H₁₆F₆O₄+Na]⁺ 409.0850, found 409.0851.

IR (film): 2953, 1761, 1610, 1592, 1485, 1460, 1431, 1372, 1282, 1216, 1163, 1134, 1103 cm⁻¹.

5.3.26 3-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1H-inden-5-yl acetate (**16c**)

The reaction was performed following the general protocol as in **5.3.21**, but using alkene **138c** (0.094 g, 0.50 mmol), HTIB (0.235 g, 0.60 mmol) and TFE (10 mL) at 0 °C for 5 min.²⁷ The crude product was purified by flash column chromatography (4-5 % EtOAc in hexane), giving acetal **16c** (0.126 g, 0.330 mmol, 65%) as white solid (MP: 63.6-65.2 °C).

3-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1H-inden-5-yl acetate (16c)

^1H NMR (300 MHz, CDCl_3) δ : 1.98-2.09 (m, 1H), 2.21-2.33 (m, 1H), 2.28 (s, 3H), 2.79-2.99 (m, 2H), 3.46 (q, $J = 7.8$ Hz, 1H), 3.85-4.06 (m, 2H), 4.69 (d, $J = 8.4$ Hz, 1H), 6.91 (ddd, $J = 8.1, 2.1, 0.3$ Hz, 1H), 7.10 (d, $J = 1.8$ Hz, 1H), 7.20 (d, $J = 8.1$ Hz, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ : 21.1 (CH_3), 27.5 (CH_2), 30.6 (CH_2), 61.7 (q, $J = 34.8$ Hz) (CH_2), 63.5 (q, $J = 34.8$ Hz) (CH_2), 105.1 (CH), 118.9 (CH), 120.9 (CH), 123.6 (q, $J = 276$ Hz) (CF_3), 123.7 (q, $J = 276$ Hz) (CF_3), 125.1 (CH), 142.0 (C), 142.2 (C), 149.5 (C), 169.8 (C).

LRMS m/z (rel. int.): 386 (M^+ , 2), 344 (25), 287 (7), 244 (8), 211 (100), 145 (17), 133 (92), 115 (15), 105 (17), 83 (29), 77 (12), 43(43).

HRMS [ESI(+)] : calcd. for $[\text{C}_{16}\text{H}_{16}\text{F}_6\text{O}_4+\text{Na}]^+$ 409.0850, found 409.0851.

IR (film): 2919, 2850, 1760, 1610, 1591, 1540, 1484, 1459, 1429, 1372, 1281, 1214 cm^{-1} .

5.3.27 N-(1-(Dimethoxymethyl)-2,3-dihydro-1H-inden-5-yl)benzamide (7m)

The reaction was performed following the general protocol as in **5.3.22**, but using alkene **1m** (0.125 g, 0.500 mmol), HTIB (0.235 g, 0.60 mmol) and MeOH/DCM (8:1) (10 mL) at 0 °C for 15 min.²⁷ After workup solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (30-40 % EtOAc in hexane) giving acetal **7m** (0.12 g, 0.39 mmol, 77%) as yellowish white solid (MP: 96-97.5 °C).

N-(1-(dimethoxymethyl)-2,3-dihydro-1H-inden-5-yl)benzamide (7m)

^1H NMR (300 MHz, CDCl_3) δ : 1.92-2.04 (m, 1H), 2.15-2.27 (m, 1H), 2.78-2.99 (m, 2H), 3.37-3.47 (m, 1H), 3.38 (s, 3H), 3.42 (s, 3H), 4.29 (d, $J = 7.5$ Hz, 1H), 7.29 (dd, 8.1, 2.1 Hz, 1H), 7.38 (d, $J = 8.4$ Hz, 1H), 7.42-7.55 (m, 3H), 7.61 (s, 1H), 7.83-7.86 (m, 2H), 7.93 (bs, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ : 27.5 (CH_2), 31.4 (CH_2), 46.9 (CH), 52.8 (CH_3), 54.2 (CH_3), 107.1 (CH), 116.6 (CH), 118.5 (CH), 125.6 (CH), 126.9 (CH), 128.5 (CH), 131.5 (CH), 134.9 (C), 136.8 (C), 139.1 (C), 145.7 (C), 165.8 (C).

HRMS [ESI(+)]: calcd. for $[\text{C}_{19}\text{H}_{21}\text{NO}_3+\text{H}]^+$ 312.1600, found 312.1600.

IR (film): 3307, 3060, 2937, 2830, 1737, 1650, 1601, 1580, 1532, 1493, 1447, 1424, 1374, 1328, 1283, 1248, 1210, 1187, 1154, 1116 cm^{-1} .

5.3.28 (9H-Fluoren-9-yl)methyl (1-(dimethoxymethyl)-2,3-dihydro-1H-inden-5-yl)carbamate (7o)

The reaction was performed following the general protocol as in **5.3.22**, but using alkene **1o** (0.183 g, 0.50 mmol), HTIB (0.235 g, 0.60 mmol) and MeOH/DCM (4:1) (10 mL) at 0 °C for 10 min.²⁷ The crude product was purified by flash column chromatography (15-25 % EtOAc in hexane) giving acetal **7o** (0.138 g, 0.320 mmol, 64%) as white solid (MP: 115-117 °C).

(9H-Fluoren-9-yl)methyl (1-(dimethoxymethyl)-2,3-dihydro-1H-inden-5-yl)carbamate (7o)

^1H NMR (300 MHz, CDCl_3) δ : 1.89-2.01 (m, 1H), 2.12-2.24 (m, 1H), 2.73-2.94 (m, 2H), 3.34-3.43 (m, 1H), 3.35 (s, 3H), 3.40 (s, 3H), 4.22-4.26 (m, 1H), 4.26 (d, $J = 7.5$ Hz, 1H), 4.51 (d, $J = 6.6$ Hz, 2H), 6.71 (bs, 1H), 7.04 (d, $J = 7.2$ Hz, 1H), 7.27-7.32 (m, 4H), 7.36-7.41 (m, 2H), 7.59 (d, $J = 7.5$ Hz, 2H), 7.76 (d, $J = 7.5$ Hz, 2H).

^{13}C NMR (75 MHz, CDCl_3) δ : 27.5 (CH_2), 31.4 (CH_2), 46.8 (CH), 47.0 (CH), 52.8 (CH_3), 54.1 (CH_3), 66.6 (CH_2), 107.1 (CH), 115.0 (CH), 117.0 (CH), 119.9 (CH), 124.8 (CH), 125.6 (CH), 127.0 (CH), 127.6 (CH), 136.6 (C), 138.0 (C), 141.2 (C), 143.7 (C), 145.7 (C), 153.5 (C).

HRMS [ESI(+)]: calcd. for $[\text{C}_{27}\text{H}_{27}\text{NO}_4+\text{Na}]^+$ 452.1832, found 452.1836.

IR (film): 3307, 3066, 2942, 2849, 2830, 1730, 1708, 1598, 1538, 1493, 1478, 1450, 1431, 1375, 1326, 1297, 1220 cm^{-1} .

5.3.29 1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1*H*-inden-4-yl benzoate (**16s**)

The reaction was performed following the general protocol as in **5.3.21**, but using alkene **138s** (0.125 g, 0.500 mmol), HTIB (0.235 g, 0.60 mmol) in TFE (10 mL) at 0 °C for 5 min.²⁷ The crude product was purified by flash column chromatography (3-4 % EtOAc in hexane) giving acetal **16s** (0.159 g, 0.356 mmol, 71%) as white solid (MP: 79-79.8 °C).

1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1*H*-inden-4-yl benzoate (16s**)**

¹H NMR (300 MHz, CDCl₃) δ: 1.99-2.11 (m, 1H), 2.20-2.32 (m, 1H), 2.76-2.97 (m, 2H), 3.54 (q, *J* = 8.1 Hz, 1H), 3.85-4.09 (m, 4H), 4.74 (d, *J* = 8.1 Hz, 1H), 7.10 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.48-7.54 (m, 2H), 7.64 (tt, *J* = 7.5, 1.5 Hz, 1H), 8.18-8.22 (m, 2H).

¹³C NMR (75 MHz, CDCl₃) δ: 26.8 (CH₂), 28.2 (CH₂), 47.6 (CH), 61.9 (q, *J* = 34.8 Hz) (CH₂), 63.4 (q, *J* = 34.8 Hz) (CH₂), 105.1 (CH), 120.7 (CH), 123.2 (CH), 123.69 (q, *J* = 276 Hz) (CF₃), 123.74 (q, *J* = 276 Hz) (CF₃), 128.1 (CH), 128.6 (CH), 129.4 (C), 130.2 (CH), 133.6 (CH), 136.8 (C), 143.4 (C), 147.4 (C), 164.5 (C).

HRMS [ESI(+)]: calcd. for [C₂₁H₁₈F₆O₄+Na]⁺ 471.1007, found 471.1010.

IR (film): 3067, 2948, 1738, 1602, 1585, 1469, 1453, 1423, 1383, 1279, 1230, 1168, 1134 cm⁻¹.

5.3.30 (1*R*,3*S*)-1-(bis(2,2,2-trifluoroethoxy)methyl)-3-(3,4-dichlorophenyl)-2,3-dihydro-1*H*-indene (**16f**)

The reaction was performed following the general protocol as in **5.3.21**, but using alkene **1f** (0.137 g, 0.500 mmol), HTIB (0.235 g, 0.60 mmol) and TFE/DCM (1:4) (10 mL) at 0 °C for 5 min.²⁷ The crude product was purified by flash column chromatography (3-4 % EtOAc in hexane) giving acetal **16f** (0.149 g, 0.315 mmol, 63%, *d.r.* 20:1) as colorless oil.

(1*R*,3*S*)-1-(bis(2,2,2-trifluoroethoxy)methyl)-3-(3,4-dichlorophenyl)-2,3-dihydro-1*H*-indene (16f)

¹H NMR (300 MHz, CDCl₃) δ: 2.11-2.21 (m, 1H), 2.57-2.66 (m, 1H), 3.56-3.63 (m, 1H), 3.82-4.08 (m, 4H), 4.41 (t, *J* = 8.1 Hz, 1H), 4.73 (d, *J* = 7.8 Hz, 1H), 6.93-6.99 (m, 2H), 7.20 (d, *J* = 2.1 Hz, 1H), 7.24-7.29 (m, 2H), 7.35 (d, *J* = 9.0 Hz, 1H), 7.43-7.45 (m, 1H).

¹³C NMR (75 MHz, CDCl₃) δ: 37.5 (CH₂), 46.4 (CH), 49.0 (CH), 62.0 (q, *J* = 34.9 Hz) (CH₂), 63.9 (q, *J* = 34.7 Hz) (CH₂), 105.1 (CH), 123.62 (q, *J* = 276 Hz) (CF₃), 123.66 (q, *J* = 276 Hz) (CF₃), 125.2 (CH), 125.9 (CH), 127.3 (CH), 127.5 (CH), 128.3 (CH), 129.8 (CH), 130.5 (CH), 132.6 (C), 141.0 (C), 145.3 (C), 146.0 (C).

Anal. Calcd for C₂₀H₁₆Cl₂F₆O₂: C, 50.76; H, 3.41. Found: C, 50.55; H, 3.43.

IR (film): 3077, 2943, 1590, 1561, 1469, 1421, 1401, 1280, 1167, 1133 cm⁻¹.

5.3.31 ((1*R*,3*R*)-3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-inden-1-yl)metanol (17f)

Alkene **1f** (0.137 g, 0.500 mmol) at 0 °C was stirred with HTIB (0.215 g, 0.550 mmol) in HFIP/DCM (1:4) (10 mL), H₂O (22 equiv. 0.2 mL). After 5 min NaBH₄ (5 equiv) was added.²⁷ This mixture was stirred for 2 h at rt. H₂O was added, extracted with DCM (3 x 10 mL) washed with brine (2 x 10 mL), dried over anhydrous MgSO₄. The solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (12-25% EtOAc in hexane) gave alcohol **17f** (0.10 g, 0.34 mmol, 68%) as colorless oil.

((1R,3R)-3-(3,4-Dichlorophenyl)-2,3-dihydro-1H-inden-1-yl)methanol (17f)

^1H NMR (300 MHz, CDCl_3) δ : 1.66 (bs, 1H), 2.14-2.24 (m, 1H), 2.47-2.55 (m, 1H), 3.44-3.52 (m, 1H), 3.80 (d, J = 6.3 Hz, 2H), 4.42 (t, J = 7.8 Hz, 1H), 6.95-7.00 (m, 2H), 7.18-7.28 (m, 3H), 7.35 (d, J = 8.4 Hz, 2H).

^{13}C NMR (75 MHz, CDCl_3) δ : 39.3 (CH_2), 46.5 (CH), 49.2 (CH), 65.9 (CH_2), 124.4 (CH), 125.2 (CH), 127.3 (CH), 127.4 (CH), 127.7 (CH), 129.8 (CH), 130.2 (C), 130.4 (CH), 132.4 (C), 143.9 (C), 145.9 (C), 146.1 (C).

HRMS [ESI(+)]: calcd. for $[\text{C}_{16}\text{H}_{14}\text{Cl}_2\text{O}+\text{K}]^+$ 331,0059, found 331,0043.

IR (film): 3392, 3067, 3022, 2929, 2868, 1736, 1589, 1560, 1468, 1398, 1373, 1324, 1246 cm^{-1} .

5.3.32 (1R,3S)-1-(3,4-Dichlorophenyl)-3-(dimethoxymethyl)-2,3-dihydro-1H-indene (7f)

The reaction was performed following the general protocol as in **5.3.22**, but using alkene **1f** (0.137 g, 0.500 mmol), HTIB (0.705 g, 1.80 mmol) and MeOH (10 mL) at 0 °C for 5 min. The crude product was purified by flash column chromatography (3-4 % EtOAc in hexane) giving acetal **7f** (0.108 g, 0.321 mmol, 64%) as colorless oil.²⁷

(1R,3S)-1-(3,4-dichlorophenyl)-3-(dimethoxymethyl)-2,3-dihydro-1H-indene (7f)²⁷

^1H NMR (300 MHz, CDCl_3) δ : 2.06-2.16 (m, 1H), 2.55-2.63 (m, 1H), 3.34 (s, 3H), 3.43 (s, 3H), 3.53-3.60 (m, 1H), 4.35 (d, J = 6.9 Hz, 1H), 4.40 (t, J = 8.1 Hz, 1H), 6.93-6.96 (m, 1H), 6.97 (ddd, J = 8.4, 2.4, 0.6 Hz, 1H), 7.16-7.26 (m, 3H), 7.33 (d, J = 8.1 Hz, 1H), 7.43-7.46 (m, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ : 37.8, 46.8, 49.2, 53.4, 54.8, 107.1, 124.8, 125.7, 127.1, 127.4, 127.5, 129.8, 130.1, 130.4, 132.4, 143.0, 146.0, 146.2.

5.3.33 (1*R*,3*R*)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-3-methyl-2,3-dihydro-1*H*-indene

(16b)

The reaction was performed following the general protocol as in **5.3.21**, but using alkene **1b** (0.047 g, 0.30 mmol) HTIB (0.141 g, 0.360 mmol) and TFE/DCM (6 mL) at 0 °C for 5 min. The crude product was purified by flash column chromatography (3-4 % EtOAc in hexane) giving acetal **16b** (0.065 g, 0.19 mmol, 63%, *d.r.* 12:1) as colorless oil.²⁷

(1*R*,3*R*)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-3-methyl-2,3-dihydro-1*H*-indene (**16b**)²⁷

¹H NMR (300 MHz, CDCl₃) δ: 1.26 (d, *J* = 6.9 Hz, 3H), 1.76-1.86 (m, 1H), 2.27-2.36 (m, 1H), 3.27 (sext, *J* = 7.2 Hz, 1H), 3.46 (sext, *J* = 4.2 Hz, 1H), 3.82-4.05 (m, 4H), 4.64 (d, *J* = 8.4 Hz, 1H), 7.15-7.28 (m, 3H), 7.35 (d, *J* = 6.9 Hz, 1H).

¹³C NMR (75 MHz, CDCl₃) δ: 20.5 (CH₃), 35.9 (CH₂), 37.6 (CH), 45.9 (CH), 61.5 (q, *J* = 34.7 Hz) (CH₂), 63.8 (q, *J* = 34.7) (CH₂), 105.0 (CH), 123.6 (q, *J* = 276 Hz) (CF₃), 123.5 (CH), 123.8 (q, *J* = 276 Hz) (CF₃), 125.8 (CH), 126.6 (CH), 127.8 (CH), 140.3 (C), 149.2 (C).

5.3.34 (1*R*,3*R*)-1-(Dimethoxymethyl)-3-methyl-2,3-dihydro-1*H*-indene (**7b**)

The reaction was performed following the general protocol as in **5.3.22**, but using alkene **1b** (0.058 g, 0.40 mmol), HTIB (0.313 g, 0.800 mmol) and MeOH (8 mL) at 0 °C for 5 min. The crude product was purified by flash column chromatography (3-4 % EtOAc in hexane) giving acetal **7b** (0.051 g, 0.250 mmol, 62%) as colorless oil.²⁷

(1*R*,3*R*)-1-(Dimethoxymethyl)-3-methyl-2,3-dihydro-1*H*-indene (**7b**)²⁷

^1H NMR (300 MHz, CDCl_3) δ : 1.25 (d, $J = 6.9$ Hz, 3H), 1.72-1.82 (m, 1H), 2.24-2.33 (m, 1H), 3.26 (sext, $J = 7.2$ Hz, 1H), 3.35 (s, 3H), 3.39 (s, 3H), 3.41-3.49 (m, 1H), 4.27 (d, $J = 7.5$ Hz, 1H), 7.12-7.22 (m, 3H), 7.37 (m, 1H).

^{13}C NMR (75 MHz, CDCl_3) δ : 20.6, 36.3, 37.7, 46.2, 52.9, 54.5, 107.0, 123.2, 125.7, 126.2, 127.0, 142.3, 149.4.

5.3.35 ((1*R*,3*S*)-3-Methyl-2,3-dihydro-1*H*-inden-1-yl)methanol (**17b**)

The reaction was performed following the general protocol as in **5.3.31**, but using alkene **1b** (0.072 g, 0.50 mmol), HTIB (0.215 g, 0.550 mmol) HFIP/DCM (1:4) (10 mL) at 0 °C for 5 min. NaBH_4 (5 equiv) was added after 5 min.²⁷ The crude product was purified by flash column chromatography (12-15 % ethyl acetate in hexane) giving alcohol **17b** (0.149 g, 0.315 mmol, 63%, *d.r.* 13:1) as colorless oil.

((1*R*,3*S*)-3-Methyl-2,3-dihydro-1*H*-inden-1-yl)methanol (**17b**)

^1H NMR (300 MHz, CDCl_3) δ : 1.27 (d, $J = 6.9$ Hz, 3H), 1.62 (bs, 1H), 1.77-1.87 (m, 1H), 2.16-2.24 (m, 1H), 3.22-3.38 (m, 2H), 3.71 (d, $J = 6.6$ Hz, 2H), 7.14-7.27 (m, 4H).

^{13}C NMR (75 MHz, CDCl_3) δ : 20.4 (CH_3), 37.5 (CH_2), 37.7 (CH), 46.2 (CH), 66.1 (CH_2), 123.6 (CH), 124.3 (CH), 126.3 (CH), 127.2 (CH), 143.4 (C), 149.2 (C).

HRMS [ESI(+)] : calcd. for $[\text{C}_{11}\text{H}_{14}\text{O}+\text{Na}]^+$ 185.0942, found 185.0936.

LRMS m/z (rel. int.): 162 ($\text{M}^{+\bullet}$, 12), 144 (11), 132 (11), 131 (100), 129 (30), 115 (24), 91 (29), 77 (7), 63 (5), 51 (6), 39 (4).

5.3.36 (1,2,3,4-Tetrahydronaphthalen-1-yl)methanol (**191a**)

The reaction was performed following the general protocol as in **5.3.31**, but using alkene **87a** (0.150 g, 1.04 mmol), HTIB (0.448g, 1.14 mmol), HFIP/DCM (1:6) (20 mL) and H₂O 22 equiv at 0 °C. NaBH₄ was added in excess (5 equiv).²⁷ Purification by flash column chromatography (10-20% EtOAc in hexane) gave alcohol **191a** (0.109 g, 0.672 mmol, 65%) as colorless oil.

(1,2,3,4-Tetrahydronaphthalen-1-yl)methanol (191a)¹⁴³

¹H NMR (200 MHz, CDCl₃) δ: 1.54 (bs, 1H), 1.65-1.96 (m, 4H), 2.76 (t, *J* = 6.2 Hz, 2H), 2.98 (quint, *J* = 5.8 Hz, 1H), 3.80 (d, *J* = 6.4 Hz, 2H), 7.08-7.25 (m, 4H).

¹³C NMR (50 MHz, CDCl₃) δ: 19.8, 25.2, 29.7, 40.3, 67.1, 125.7, 126.1, 128.7, 129.3, 136.6, 138.1.

5.3.37 (2,3-Dihydro-1H-inden-1-yl)methanol (17a)

The reaction was performed following the general protocol as in **5.3.31**, but using alkene **1a** (0.325 g, 2.50 mmol), HTIB (0.108 g, 2.75 mmol), HFIP/DCM (1:4) (50 mL) and H₂O 22 equiv at 0 °C for 5 min. NaBH₄ (5 equiv) was added after 5 min. The crude product was purified by flash column chromatography (12-15 % ethyl acetate in hexane) giving alcohol **17a** (0.248 g, 1.67 mmol, 67%) as colorless oil.²⁷

2,3-Dihydro-1H-inden-3-yl)methanol (17a)²⁷

¹H NMR (200 MHz, CDCl₃) δ: 1.56 (bs, 1H), 1.85-2.02 (m, 1H), 2.18-2.36 (m, 1H), 2.80-3.10 (m, 2H), 3.30-3.42 (m, 1H), 3.80 (d, *J* = 6.2 Hz, 2H), 7.15-7.30 (m, 4H).

¹³C NMR (50 MHz, CDCl₃) δ: 28.4, 31.4, 47.5, 66.0, 124.1, 124.7, 126.2, 127.0, 143.8, 144.7.

5.4 *In situ* generation of HTIB for oxidative rearrangement

5.4.1 (1,2,3,4-Tetrahydronaphthalen-4-yl)methanol (**191a**). General Procedure A: *In situ* generation of HTIB for oxidative rearrangement of alkenes followed by reduction with NaBH₄.

To a stirred solution of PhI (0.204 g, 0.114 mL, 1.00 mmol) in HFIP/DCM (1:6) (5 mL) was added *m*CPBA (77%, 0.224 g, 1.00 mmol), followed by TsOH.H₂O (0.19 g, 1.0 mmol). The resulting solution was stirred at rt for 30 min. H₂O (0.40 mL, 22 mmol) and alkene **87a** (0.115 g, 0.800 mmol) was added at 0 °C. After 2 min, NaBH₄ (0.19 g, 5.0 mmol) was added. The mixture was stirred for 2 h. The reaction was quenched with saturated solution of NaHCO₃, extracted with EtOAc, washed with brine and dried over anhydrous MgSO₄. The solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (10-20%, EtOAc in hexane) giving alcohol **191a**¹⁴³ (0.920 g, 0.570 mmol, 71%) as colorless oil.

(1,2,3,4-Tetrahydronaphthalen-4-yl)methanol (**191a**)¹⁴³

¹H NMR (200 MHz, CDCl₃) δ: Data given above

¹³C NMR (50 MHz, CDCl₃) δ: Data given above

5.4.2 (3,4-Dihydro-2H-chromen-4-yl)methanol (**191b**)

The reaction was performed following General Procedure A, using PhI (0.204 g, 0.114 mL, 1.00 mmol), *m*CPBA (77%, 0.224 g, 1.00 mmol) and TsOH.H₂O (0.19 g, 1.0 mmol) in

HFIP/DCM (1:6) (5 mL). After 30 min, H₂O (0.40 mL, 22 mmol) and alkene **87b** (0.118 g, 0.810 mmol) was added at 0 °C. NaBH₄ (0.19 g, 5.0 mmol) was added after 2 min. Purification by flash column chromatography (10-20% EtOAc in hexane) gave compound **191b** (0.11 g, 0.67 mmol, 83%) as colorless oil.

(3,4-Dihydro-2H-chromen-4-yl)methanol (191b)

¹H NMR (300 MHz, CDCl₃) δ: Data given above

¹³C NMR (75 MHz, CDCl₃) δ: Data given above

5.4.3 (2,3-Dihydro-1H-inden-1-yl)methanol (17a)

The reaction was performed following general procedure A, but using PhI (0.490 g, 0.274 mL, 2.40 mmol), *m*CPBA (77%, 0.538 g, 2.40 mmol) and TsOH.H₂O (0.456 g, 2.40 mmol) in HFIP/DCM (1:6) (10 mL). After 30 min, H₂O (0.40 mL, 22 mmol) and alkene **1a** (0.270 g, 2.08 mmol) was added at 0 °C. NaBH₄ (0.19 g, 5.0 mmol) was added. Purification by flash column chromatography (10-20% EtOAc in hexane) gave alcohol **17a** (0.202 g, 1.36 mmol, 65%) as colorless oil.

(2,3-Dihydro-1H-inden-3-yl)methanol (17a)²⁷

¹H NMR (200 MHz, CDCl₃) δ: Data given above

¹³C NMR (50 MHz, CDCl₃) δ: Data given above

5.4.4 8,9-Dihydro-5H-benzo[7]annulen-6(7H)-one (216). General Procedure B: *In situ* generation of HTIB for oxidative rearrangement of alkenes

The reaction was performed, using PhI (0.204 g, 0.114 mL, 1.00 mmol), *m*CPBA (77%, 0.224 g, 1.00 mmol) and TsOH.H₂O (0.19 g, 1.0 mmol) in HFIP/DCM (1:6) (5 mL). After 30 min, H₂O (0.40 mL, 22 mmol) and alkene **139** (0.125 g, 0.870 mmol) was added at 0 °C. The reaction was quenched with saturated solution of NaHCO₃, extracted with EtOAc, washed with brine and dried over anhydrous MgSO₄. Purification by flash column chromatography (5-8% EtOAc in hexane) gave compound **216**³⁰ (0.135 g, 0.840 mmol, 97%) as colorless oil.

8,9-Dihydro-5*H*-benzo[7]annulen-6(7*H*)-one (216**)**³⁰

¹H NMR (200 MHz, CDCl₃) δ: 1.99 (m, 2H), 2.57 (t, *J* = 7 Hz, 2H), 2.92-2.98 (m, 2H), 3.73 (s, 2H), 7.12-7.23 (m, 4H).

¹³C NMR (50 MHz, CDCl₃) δ: 26.2, 32.9, 43.6, 50.1, 127.1, 127.5, 129.2, 129.5, 133.5, 140.4, 208.6.

5.4.5 1-Phenylpropan-2-one (218**)**

The reaction was performed following the General Procedure B, but using PhI (0.204 g, 0.114 mL, 1.00 mmol), *m*CPBA (77%, 0.224 g, 1.00 mmol) and TsOH.H₂O (0.19 g, 1.0 mmol) in HFIP/DCM (1:6) (5 mL). After 30 min, H₂O (0.40 mL, 22 mmol) and alkene **217** (0.094 g, 0.80 mmol) was added at 0 °C. Purification by flash column chromatography (5-8% EtOAc in hexane) gave compound **218**²³ (0.087 g, 0.65 mmol, 81%) as colorless oil.

1-Phenylpropan-2-one (218**)**²³

¹H NMR (200 MHz, CDCl₃) δ: 2.14 (s, 3H), 3.69 (s, 2H), 7.18-7.22 (m, 2H), 7.26-7.38 (m, 3H).

¹³C NMR (50 MHz, CDCl₃) δ: 29.2, 50.9, 126.9, 128.6, 129.3, 134.2, 206.2.

5.4.6 **1-(1,2,3,4-Tetrahydronaphthalen-4-yl)ethanone (195aa). General Procedure C: *In situ* generation of HTIB for ring contraction of methyl substituted cyclic alkenes**

To a stirred solution of PhI (0.204 g, 0.114 mL, 1.00 mmol) in TFE/DCM (1:1) (5 mL) was added *m*CPBA (77%) (0.224 g, 1.00 mmol) followed by TsOH.H₂O (0.19 g, 1.0 mmol). The resulting solution was stirred at rt for 30 min. To this mixture alkene **87aa** (0.127 g, 0.800 mmol) was added at 0 °C. The reaction was quenched with NaHCO₃, extracted with EtOAc, washed with brine and dried over anhydrous MgSO₄. The solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (5-7% EtOAc in hexane), giving ketone **195aa**²⁷ (0.111 g, 0.640 mmol, 79%) as colorless liquid.

1-(1,2,3,4-tetrahydronaphthalen-4-yl)ethanone (195aa)²⁷

¹H NMR (200 MHz, CDCl₃) δ: 1.62-2.35 (m, 4H), 2.12 (s, 3H), 2.76-2.82 (m, 2H), 3.82 (t, *J* = 6.6 Hz, 1H), 6.95-7.00 (m, 1H), 7.10-7.23 (m, 3H).

5.4.7 **1-(3,4-Dihydro-2H-chromen-4-yl)ethanone (195bb)**

The reaction was performed following General Procedure C, but using PhI (0.204 g, 0.114 mL, 1.00 mmol), *m*CPBA (77%, 0.224 g, 1.00 mmol) and TsOH.H₂O (0.19 g, 1.0 mmol) in TFE/DCM (1:1) (5 mL). After 30 min, alkene **87bb** (0.135 g, 0.840 mmol) was added at 0 °C. Purification by flash column chromatography (5-7% EtOAc in hexane) gave ketone **195bb** (0.091 g, 0.51 mmol, 61%) as colorless oil.

1-(3,4-Dihydro-2H-chromen-4-yl)ethanone (195bb)

¹H NMR (300 MHz, CDCl₃) δ: Data given above

^{13}C NMR (75 MHz, CDCl_3) δ : Data given above

5.4.8 1-(2,3-Dihydro-1*H*-inden-1-yl)ethanone (**15aa**)

The reaction was performed following General procedure C, but using PhI (0.073 g, 0.041 mL, 0.36 mmol), *m*CPBA (77%, 0.081 g, 0.36 mmol) and $\text{TsOH}\cdot\text{H}_2\text{O}$ (0.068 g, 0.31 mmol) in TFE/DCM (1:1) (2 mL). After 30 min, alkene **1aa** (0.044 g, 0.30 mmol) was added at 0 °C. Purification by flash column chromatography (5-7% EtOAc in hexane) gave compound **15aa**²⁷ (0.035 g, 0.22 mmol, 73%) as colorless oil.

1-(2,3-Dihydro-1*H*-inden-1-yl)ethanone (**15aa**)²⁷

^1H NMR (300 MHz, CDCl_3) δ : 2.18 (s, 3H), 2.30-2.37 (m, 2H), 2.90-3.00 (m, 1H), 3.04-3.14 (m, 1H), 4.09 (t, $J = 7.2$ Hz, 1H), 7.18-7.30 (m, 4H).

^{13}C NMR (75 MHz, CDCl_3) δ : 27.6, 28.5, 31.8, 58.8, 124.7, 124.8, 126.4, 127.4, 140.7, 144.4, 208.7.

5.4.9 1-Methyl-2-tetralone (**209aa**)

To a stirred solution of **1aa** (0.115 g, 0.800 mmol) in TFE/DCM (1:4) (5 mL) at 0 °C was added *m*CPBA (77%, 0.224 g, 1.00 mmol) and $\text{TsOH}\cdot\text{H}_2\text{O}$ (0.19 g, 1.0 mmol). After 20 min, the reaction was quenched with NaHCO_3 . Purification by flash column chromatography (7-10% EtOAc in hexane) gave ketone **209aa**³⁰ (0.104 g, 0.650 mmol, 81 %) as colorless oil.

1-Methyl-2-tetralone (**209aa**)³⁰

^1H NMR (200 MHz, CDCl_3) δ : 1.47 (d, $J = 7$ Hz, 3H), 2.39-2.71 (m, 2H), 3.05-3.12 (m, 2H), 3.52 (q, $J = 7$ Hz, 1H), 7.18-7.31 (m, 4H).

^{13}C NMR (50 MHz, CDCl_3) δ : 14.1, 27.9, 37.1, 47.4, 126.0, 126.6, 126.9, 127.4, 136.7, 137.9, 212.3.

5.4.10 Reaction of 6,7-dihydro-5H-benzo[7]annulene (**191a**) with *In situ* generation of Iodine(III) from $p\text{-C}_6\text{H}_4\text{I}_2$

The reaction was performed following general procedure A, using $p\text{-C}_6\text{H}_4\text{I}_2$ (0.165 g, 0.500 mmol), $m\text{CPBA}$ (77%, 0.224 g, 1.00 mmol) and $\text{TsOH}\cdot\text{H}_2\text{O}$ (0.19 g, 1.0 mmol) in HFIP/DCM (1:6) (5 mL). After 2 h H_2O (0.4 mL, 22 mmol) and alkene **87a** (0.124 g, 0.860 mmol) were added at 0 °C. Purification by flash column chromatography (10-20% EtOAc in hexane) gave alcohol **191a**¹⁴³ (0.089 g, 0.55 mmol, 63%) as colorless oil.

(1,2,3,4-tetrahydronaphthalen-1-yl)methanol (**191a**)¹⁴³

^1H NMR (200 MHz, CDCl_3) δ : Data given above

^{13}C NMR (50 MHz, CDCl_3) δ : Data given above

5.5 Asymmetric ring contraction reactions mediated by chiral I(III)

5.5.1 (*R*)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1H-indene (**16a**)

To a stirred solution of Ar^*I (*R,R*)-**36a** (0.872 g, 2.00 mmol) in TFE/DCM (1:40) (17 mL) was added $m\text{CPBA}$ (77%) (0.448 g, 2.00 mmol) followed by (+)- CSA (0.464 g, 2.00 mmol). The resulting solution was stirred at rt for 30 min. Solvent was removed under reduced pressure. To this reaction mixture TFE/DCM (1:4) (17 mL) was added and the temperature was lowered to -78 °C, followed by addition of alkene **1a** (0.130 g, 1.00 mmol) (dissolved in 3 mL of

TFE/DCM (1:4)). After 5 min the reaction was quenched with saturated solution of NaHCO_3 , extracted with DCM, washed with brine and dried over anhydrous MgSO_4 . The solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (2-3%, EtOAc in hexane), giving acetal **16a** (0.196 g, 0.110 mmol, 60%) as colorless oil in 58% *ee* (Daicel chiral ODH column (25 cm), hexanes/*i*-PrOH = 99.7/0.3, 0.3 mL/min, temp 28°C, 215 nm; tr (major) = 40.3 min, tr (minor) = 46.4 min), $[\alpha]_D^{20} = +6.5$ ($c = 0.35$, CHCl_3).

(*R*)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1*H*-indene (16a)²⁷

^1H NMR (300 MHz, CDCl_3) δ : Data given above

^{13}C NMR (75 MHz, CDCl_3) δ : Data given above

5.5.2 (*R*)-(2,3-Dihydro-1*H*-inden-1-yl)metanol (17a)

To a stirred solution of Ar*I (*R,R*)-**36a** (0.872 g, 2.00 mmol) in HFIP/ CH_2Cl_2 (1:40) (17 mL) was added *m*CPBA (77%) (0.448 g, 2.00 mmol) followed by (+)-CSA (0.464 g, 2.0 mmol). The resulting solution was stirred at rt for 30 min. H_2O (0.4 mL) and alkene **1a** (0.130 g, 1.0 mmol) (dissolved in 3 mL of HFIP/DCM (1:40)) was added at -78 °C. After 2 min, NaBH_4 (0.190 g, 5.0 mmol) was added. The reaction stirred for 2 h at rt. The reaction was quenched with saturated solution of NaHCO_3 , extracted with DCM (3 x 10 mL), washed with brine (2 x 10 mL) and dried over anhydrous MgSO_4 . The solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (10-20%, EtOAc in hexane), giving alcohol **17a** (0.050 g, 0.34 mmol, 34%) in 60% *ee* as colorless oil (chiral column ALPHA DEXTM 120 FUSED SILICA Capillary Column (30m x 0.25mm x 0.25 μm), tr (major) = 25.7 min, tr (minor) = 26.3 min), $[\alpha]_D^{20} = +8.8$ ($c = 1$, CHCl_3).

(*R*)-(2,3-Dihydro-1*H*-inden-1-yl)metanol (17a)²⁷

^1H NMR (200 MHz, CDCl_3) δ : Data given above

^{13}C NMR (50 MHz, CDCl_3) δ : Data given above

5.5.3 (*R*)-*N*-(1-(Dimethoxymethyl)-2,3-dihydro-1*H*-inden-5-yl)acetamide (**7l**)

To a stirred solution of Ar^*I (*R,R*)-**36a** (0.872 g, 2.00 mmol) in TFE/DCM (1:40) (17 mL) was added *m*CPBA (77%) (0.448 g, 2.00 mmol) followed by (+)-CSA (0.464 g, 2.00 mmol). The resulting solution was stirred at rt for 30 min. Solvent was removed under reduced pressure. To this reaction mixture DCM (15 mL) and MeOH (1.7 mL) was added and the temperature was lowered to $-78\text{ }^\circ\text{C}$, followed by addition of alkene **1l** (0.187 g, 1.00 mmol) (dissolved in 3 mL DCM/MeOH (10:1)). After 5 min the reaction was quenched with saturated solution of NaHCO_3 , extracted with DCM, washed with brine and dried over anhydrous MgSO_4 . The solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (30-60%, EtOAc in hexane), giving acetal **7l** (0.149 g, 0.600 mmol, 60%) as viscous colorless liquid in 64% *ee* (Daicel chiral ASH column (25 cm), hexanes/EtOH:MeOH (1:1) = 95/5, 1.0 mL/min, temp $28\text{ }^\circ\text{C}$, 215 nm; *tr* (minor) = 15.7 min, *tr* (major) = 16.7 min), $[\alpha]_{\text{D}}^{20} = +13.1$ ($c = 0.59$, CHCl_3).

(*R*)-*N*-(1-(Dimethoxymethyl)-2,3-dihydro-1*H*-inden-5-yl)acetamide (**7l**)²⁷

^1H NMR (300 MHz, CDCl_3) δ : Data given above

^{13}C NMR (75 MHz, CDCl_3) δ : Data given above

5.5.4 (*R*)-*N*-(1-(Dimethoxymethyl)-2,3-dihydro-1*H*-inden-5-yl)benzamide (**7m**)

The reaction was performed following the general procedure in **5.5.3**, using Ar*I (*R,R*)-**36a** (0.872 g, 2.00 mmol), *m*CPBA (77%) (0.448 g, 2.00 mmol) and (+)-CSA (0.464 g, 2.00 mmol) in TFE/DCM (1:40) (17 mL). After evaporation of the solvent, DCM (15 mL) and MeOH (1.7 mL) was added, followed by addition of alkene **1m** (0.249 g, 1.00 mmol) (dissolved in 3 mL DCM/MeOH (10:1)) at -78 °C. After workup solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (30-40 % EtOAc in hexane) giving acetal **7m** (0.221 g, 0.710 mmol, 71%) as white solid (MP: 91.5-93 °C) in 58% *ee* (Daicel chiral ASH column (25 cm), hexanes/EtOH:MeOH (1:1) = 92/8, 1.0 mL/min, temp 28°C, 220 nm; tr (minor) = 25.1 min, tr (major) = 27.5 min) $[\alpha]_D^{20} = +11.2$ ($c = 0.28$, CHCl₃).

(*R*)-*N*-(1-(dimethoxymethyl)-2,3-dihydro-1*H*-inden-5-yl)benzamide (7m)

¹H NMR (300 MHz, CDCl₃) δ: Data given above

¹³C NMR (75 MHz, CDCl₃) δ: Data given above

HRMS [ESI(+)] calcd. for [C₁₉H₂₁NO₃+Na]⁺ 334.1419, found 334.1408.

5.5.5 (9*H*-Fluoren-9-yl)methyl (*R*)-(1-(dimethoxymethyl)-2,3-dihydro-1*H*-inden-5-yl)carbamate (7o)

The reaction was performed following the general procedure in **5.5.3**, using Ar*I (*R,R*)-**36a** (0.872 g, 2.00 mmol), *m*CPBA (77%) (0.448 g, 2.00 mmol) and (+)-CSA (0.464 g, 2.00 mmol) in TFE/DCM (1:40) (17 mL). After evaporation of the solvent, DCM (15 mL) and MeOH (1.7 mL) was added, followed by addition of alkene **1o** (0.367 g, 1.00 mmol) (dissolved in 3 mL DCM/MeOH (10:1)) at -78 °C. After workup solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (20-30 % EtOAc in hexane) giving acetal **7o** (0.321 g, 0.750 mmol, 75%) as white solid (MP: 111-112 °C) in 58% *ee*, $[\alpha]_D^{20} = +7.9$ ($c = 0.29$, CHCl₃).

(9H-Fluoren-9-yl)methyl (R)-(1-(dimethoxymethyl)-2,3-dihydro-1H-inden-5-yl)carbamate (7o)

^1H NMR (300 MHz, CDCl_3) δ : Data given above

^{13}C NMR (75 MHz, CDCl_3) δ : Data given above

HRMS [ESI(+)] calcd. for $[\text{C}_{27}\text{H}_{27}\text{NO}_4+\text{Na}]^+$ 452.1832, found 452.1837.

5.5.6 (R)-N-(1-(Dimethoxymethyl)-2,3-dihydro-1H-inden-5-yl)acetamide (7l)

To a stirred solution of **7o** (0.12 g, 0.28 mmol) in dichloromethane (15 mL) was added piperidine (20% v/v) (3 mL). The solution was stirred for 25 min and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (60-70 % EtOAc in hexane) giving deprotected acetal (0.050 g, 0.241 mmol, 86%) as colourless liquid.¹⁴⁶ As deprotected amine acetal was unstable it was protected with acetyl group. The reaction was performed following the general procedure as in **5.1.22**, but using deprotected acetal (0.050 g, 0.241 mmol), cat DMAP and Ac_2O (0.08 mL, 0.82 mmol) in Et_3N (2 mL).³⁷ Purification by flash column chromatography (50-60% EtOAc in hexane) gave acetyl protected acetal **7l** (0.054 g, 0.217 mmol, 90 %) in 58% *ee* (Daicel chiral ASH column (25 cm), hexanes/ $\text{EtOH}:\text{MeOH}$ (1:1) = 95/5, 1.0 mL/min, temp 28°C , 215 nm; *tr* (minor) = 15.7 min, *tr* (major) = 16.7 min).

(R)-N-(1-(Dimethoxymethyl)-2,3-dihydro-1H-inden-5-yl)acetamide (7l)²⁷

^1H NMR (300 MHz, CDCl_3) δ : Data given above

^{13}C NMR (75 MHz, CDCl_3) δ : Data given above

5.5.7 (*R*)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1*H*-inden-4-yl acetate (**16j**)

The reaction was performed following the general procedure in **5.5.1**, using Ar*I (*R,R*)-**36a** (0.872 g, 2.00 mmol), *m*CPBA (77%) (0.448 g, 2.00 mmol) and (+)-CSA (0.464 g, 2.00 mmol) in TFE/DCM (1:40) (17 mL). After evaporation of the solvent, TFE/DCM (17 mL) (1:1) was added, followed by addition of alkene **138j** (0.188 g, 1.00 mmol) (dissolved in 3 mL TFE/DCM (1:1)) at -40 °C. After workup solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (4-5 % EtOAc in hexane) giving acetal **16j** (0.223 g, 0.580 mmol, 58%) as white solid (MP: 59.3-60.5 °C) in 64% *ee* (Daicel chiral ODH column (25 cm), hexanes/*i*-PrOH = 98.0/2.0, 0.4 mL/min, temp 26 °C, 215 nm; *tr* (major) = 18.3 min, *tr* (minor) = 21.6 min), $[\alpha]_D^{20} = +11.8$ (*c* = 0.28, CHCl₃).

(*R*)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1*H*-inden-4-yl acetate (**16j**)

¹H NMR (300 MHz, CDCl₃) δ: Data given above

¹³C NMR (75 MHz, CDCl₃) δ: Data given above

HRMS [ESI(+)] : calcd. for [C₁₆H₁₆F₆O₄+Na]⁺ 409.0850, found 409.0849.

5.5.8 (*R*)-1-(bis(2,2,2-Trifluoroethoxy)methyl)-2,3-dihydro-1*H*-inden-5-yl acetate (**16k**)

The reaction was performed following the general procedure in **5.5.1**, using Ar*I (*R,R*)-**36a** (0.872 g, 2.0 mmol), *m*CPBA (77%) (0.448 g, 2.00 mmol) and (+)-CSA (0.464 g, 2.00 mmol) in TFE/DCM (1:40) (17 mL). After evaporation of the solvent, TFE/DCM (17 mL) (1:1) was added, followed by addition of alkene **138k** (0.188 g, 1.00 mmol) (dissolved in 3 mL TFE/DCM (1:1)) at -40 °C. After workup solvent was removed under reduced pressure. The

crude product was purified by flash column chromatography (4-5 % ethyl acetate in hexane) giving acetal **16k** (0.158 g, 0.410 mmol, 41%) as colorless viscous liquid in 78% *ee* (Sigma Aldrich chiral Astec Cellulose DMP column (25 cm), hexanes/*i*-PrOH = 99.0/1.0, 0.4 mL/min, temp 28°C, 215 nm; tr (major) = 45.3 min, tr (minor) = 49.8 min), $[\alpha]_D^{20} = +13.5$ ($c = 0.58$, CHCl₃).

(*R*)-1-(bis(2,2,2-Trifluoroethoxy)methyl)-2,3-dihydro-1*H*-inden-5-yl acetate (16k)

¹H NMR (300 MHz, CDCl₃) δ : Data given above

¹³C NMR (75 MHz, CDCl₃) δ : Data given above

HRMS [ESI(+)]: calcd. for [C₁₆H₁₆F₆O₄+Na]⁺ 409.0850, found 409.0851.

5.5.9 (*R*)-3-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1*H*-inden-5-yl acetate (16c)

The reaction was performed following the general procedure in **5.5.1**, using Ar*I (*R,R*)-**36a** (0.872 g, 2.00 mmol), *m*CPBA (77%) (0.448 g, 2.00 mmol) and (+)-CSA (0.464 g, 2.00 mmol) in TFE/DCM (1:40) (17 mL). After evaporation of the solvent, TFE/DCM (17 mL) (1:1) was added, followed by addition of alkene **138c** (0.188 g, 1.00 mmol) (dissolved in 3 mL TFE/DCM (1:1)) at -40 °C. After workup solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (4-5 % ethyl acetate in hexane) giving acetal **16c** (0.204 g, 0.530 mmol, 53%) as white solid (MP: 61.2-62.1 °C) in 54% *ee* (Sigma Aldrich chiral Astec Cellulose DMP column (25 cm), hexanes/*i*-PrOH = 99.0/1.0, 0.4 mL/min, temp 26°C, 215 nm; tr (major) = 28.5 min, tr (minor) = 31.3 min) $[\alpha]_D^{20} = +4.7$ ($c = 0.48$, CHCl₃).

(*R*)-3-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1*H*-inden-5-yl acetate (16c)

¹H NMR (300 MHz, CDCl₃) δ : given above

¹³C NMR (75 MHz, CDCl₃) δ : given above

HRMS [ESI(+)]: calcd. for [C₁₆H₁₆F₆O₄+Na]⁺ 409.0850, found 409.0864.

5.5.10 (*R*)-1-(bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1*H*-inden-4-yl benzoate (**16s**)

The reaction was performed following the general procedure in **5.5.1**, using *Ar**I (*R,R*)-**36a** (0.872 g, 2.00 mmol), *m*CPBA (77%) (0.448 g, 2.00 mmol) and (+)-CSA (0.464 g, 2.00 mmol) in TFE/DCM (1:40) (17 mL). After evaporation of the solvent, TFE/DCM (17 mL) (1:1) was added, followed by addition of alkene **138s** (0.250 g, 1.00 mmol) (dissolved in 3 mL TFE/DCM (1:1)) at -40 °C. After workup solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (3-4 % ethyl acetate in hexane) giving acetal **16s** (0.272 g, 0.610 mmol, 61%) as white solid (MP: 77.5-77.9 °C) in 56% *ee*, $[\alpha]_D^{20} = +19.4$ ($c = 0.33$, CHCl₃).

(*R*)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1*H*-inden-4-yl benzoate (**16s**)

¹H NMR (300 MHz, CDCl₃) δ : given above

¹³C NMR (75 MHz, CDCl₃) δ : given above

HRMS [ESI(+)] calcd. for [C₂₁H₁₈F₆O₄+Na]⁺ 471.1007, found 471.1012.

5.5.11 (*R*)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1*H*-inden-4-yl acetate (**16j**)

To a stirred solution of acetal **16s** (0.130 g, 0.29 mmol) in methanol (15 mL) was added a solution of K₂CO₃ (0.040 g, 0.29 mmol) in H₂O (0.12 mL). The reaction mixture was stirred for 3 h. The reaction was diluted with water (5 mL), neutralized with 10% HCl and extracted with DCM (3 x 5). The extract was then washed with water (5 mL), brine (2 x 5 mL) and dried over anhydrous MgSO₄. The solvent was evaporated under reduced pressure. The crude product

was purified by flash column (10-15%, EtOAc in hexane) giving phenolic acetal (0.10 g, 0.29 mmol, 96%) as colorless oil.¹⁴⁷ The phenolic acetal was protected with acetyl group. The reaction was performed following the general procedure as in **5.1.22**, but using deprotected acetal (0.10 g, 0.29 mmol), cat DMAP and Ac₂O (0.096 ml, 0.986 mmol) in Et₃N (2 mL).²⁷ Purification by flash column chromatography (3-4% EtOAc in hexane) gave acetyl protected acetal **16j** (0.105 g, 0.272 mmol, 94%) in 56% *ee* (Daicel chiral ODH column (25 cm), hexanes/*i*-PrOH = 98.0/2.0, 0.4 mL/min, temp 26°C, 215 nm; tr (major) = 18.3 min, tr (minor) = 21.6 min).

(*R*)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1*H*-inden-4-yl acetate (16j)

¹H NMR (300 MHz, CDCl₃) δ: Data given above

¹³C NMR (75 MHz, CDCl₃) δ: Data given above

5.5.12 (1*S*,3*R*)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-3-(3,4-dichlorophenyl)-2,3-dihydro-1*H*-indene (16f) and ((1*R*,3*R*)-3-(3,4-dichlorophenyl)-2,3-dihydro-1*H*-inden-1-yl)methanol (17f)

To a stirred solution of Ar*I (*R,R*)-**36a** (0.872 g, 2.00 mmol) in TFE/DCM (1:40) (17 mL) was added *m*CPBA (77%) (0.448 g, 2.00 mmol) followed by (+)-CSA (0.464 g, 2.00 mmol). The resulting solution was stirred at rt for 30 min. Solvent was removed under reduced pressure. To this reaction mixture TFE/DCM (1:1) (17 mL) was added and the temperature was lowered to -40 °C, followed by addition of alkene **1f** (0.275 g, 1.00 mmol) (dissolved in 3 ml of TFE/DCM (1:1)). After 5 min NaBH₄ (5 equiv) (0.189 g, 5.00 mmol) was added to this reaction mixture. The reaction was stirred for 2 h at rt. The reaction was quenched with saturated

solution of NaHCO_3 , extracted with DCM, washed with brine and dried over anhydrous MgSO_4 . The solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (2-20%, EtOAc in hexane), giving acetal **16f** (0.21 g, 0.44 mmol, 44%) in 40% *ee* (Sigma Aldrich chiral Astec Cellulose DMP column (25 cm), hexanes/*i*-PrOH = 99.0/1.0, 0.5 mL/min, temp 28°C, 220 nm; tr (major) = 10.8 min, tr (minor) = 15.2 min) as colourless oil $[\alpha]_{\text{D}}^{20} = +1.8$ ($c = 0.50$, CHCl_3), and alcohol **17f** (0.128 g, 0.440 mmol, 44%) in 34% *ee* (Daicel chiral ASH column (25 cm), hexanes/EtOH:MeOH (1:1) = 98.0/2.0, 0.5 mL/min, temp 28°C, 220 nm; tr (major) = 30.3 min, tr (minor) = 32.9 min) as colorless oil, $[\alpha]_{\text{D}}^{20} = +1.6$ ($c = 0.33$, CHCl_3).

(1*S*,3*R*)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-3-(3,4-dichlorophenyl)-2,3-dihydro-1*H*-indene (16f)

^1H NMR (300 MHz, CDCl_3) δ : Data given above

^{13}C NMR (75 MHz, CDCl_3) δ : Data given above

((1*R*,3*R*)-3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-inden-1-yl)methanol (17f)

^1H NMR (300 MHz, CDCl_3) δ : Data given above

^{13}C NMR (75 MHz, CDCl_3) δ : Data given above

5.5.13 (1*R*,3*S*)-1-(3,4-Dichlorophenyl)-3-(dimethoxymethyl)-2,3-dihydro-1*H*-indene (7f)

The reaction was performed following the general procedure in 5.5.3, using Ar^*I (*R,R*)-**36a** (0.261 g, 0.600 mmol), *m*CPBA (77%) (0.134 g, 0.600 mmol) and (+)-CSA (0.139 g, 0.600 mmol) in TFE/DCM (1:40) (5 mL). After evaporation of the solvent, DCM (4.4 mL) and MeOH (0.6 mL) was added, followed by addition of alkene **1f** (0.082 g, 0.300 mmol) (dissolved in 1.5 mL DCM) at -78 °C. After 4 h reaction mixture was warm to rt. Solvent was removed under

reduced pressure. The crude product was purified by flash column chromatography (3-5 % EtOAc in hexane) giving acetal **7f** (0.017 g, 0.050 mmol, 17%) as colorless liquid in 12% *ee* (Daicel chiral ODH column (25 cm), hexanes/*i*-PrOH = 99.7/0.3, 0.5 mL/min, temp 28°C, 215 nm; tr (minor) = 17.3 min, tr (major) = 19.5 min).

(1*R*,3*S*)-1-(3,4-Dichlorophenyl)-3-(dimethoxymethyl)-2,3-dihydro-1*H*-indene (7f)

¹H NMR (300 MHz, CDCl₃) δ: Data given above

¹³C NMR (75 MHz, CDCl₃) δ: Data given above

5.5.14 (1*S*,3*S*)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-3-methyl-2,3-dihydro-1*H*-indene (16b)

and ((1*R*,3*S*)-3-methyl-2,3-dihydro-1*H*-inden-1-yl)methanol (17b)

The reaction was performed following the general procedure in **5.5.12**, using Ar*I (*R,R*)-**36a** (0.872 g, 2.00 mmol), *m*CPBA (77%) (0.448 g, 2.00 mmol) and (+)-CSA (0.464 g, 2.00 mmol) in TFE/DCM (1:40) (17 mL). After evaporation of the solvent, TFE/DCM (17 mL) (1:1) was added, followed by addition of alkene **1b** (0.144 g, 1.00 mmol) (dissolved in 3 mL TFE/DCM (1:1)) at -78 °C. After 5 min NaBH₄ (5 equiv) (0.189 g, 5.00 mmol) was added to this reaction mixture. Solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (3-15 % ethyl acetate in hexane) giving acetal **16b** (0.147 g, 0.430 mmol, 43%) in 38% *ee* (Sigma Aldrich chiral Astec Cellulose DMP column (25 cm), hexanes/*i*-PrOH = 99.5/0.5, 0.5 mL/min, temp 28°C, 220 nm; tr (major) = 11.3 min, tr (minor) = 15.7 min) as colorless oil, $[\alpha]_D^{20} = +6.7$ (*c* = 0.57, CHCl₃) and alcohol **17b** (0.055 g, 0.34 mmol, 34%) in 34% *ee* (Daicel chiral ASH column (25 cm), hexanes/EtOH:MeOH (1:1) = 99.0/1.0, 0.5 mL/min, temp 28°C, 220 nm; tr (major) = 25.3 min, tr (minor) = 33.7 min) as colorless oil, $[\alpha]_D^{20} = +1.5$ (*c* = 0.23, CHCl₃).

(1*S*,3*S*)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-3-methyl-2,3-dihydro-1*H*-indene (16b)²⁷

^1H NMR (300 MHz, CDCl_3) δ : Data given above

^{13}C NMR (75 MHz, CDCl_3) δ : Data given above

((1*R*,3*S*)-3-Methyl-2,3-dihydro-1*H*-inden-1-yl)methanol (17b)

^1H NMR (300 MHz, CDCl_3) δ : Data given above

^{13}C NMR (75 MHz, CDCl_3) δ : Data given above

HRMS [ESI(+)]: calcd. for $[\text{C}_{11}\text{H}_{14}\text{O}+\text{Na}]^+$ 185.0942, found 185.0938.

5.5.15 (1*S*,3*S*)-1-(Dimethoxymethyl)-3-methyl-2,3-dihydro-1*H*-indene (7b)

The reaction was performed following the general procedure in **5.5.3**, using Ar*I (*R,R*)-**36a** (0.261 g, 0.600 mmol), *m*CPBA (77%) (0.134 g, 0.600 mmol) and (+)-CSA (0.139 g, 0.600 mmol) in TFE/DCM (1:40) (5 mL). After evaporation of the solvent, DCM (4.4 mL) and MeOH (0.6 mL) was added, followed by addition of alkene **1b** (0.043 g, 0.30 mmol) (dissolved in 1.5 mL DCM) at -78°C . After 4 h reaction mixture was warm to rt. After workup solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (3-5 % EtOAc in hexane) giving acetal **7b** (0.032 g, 0.15 mmol, 52%) as colorless oil in 8% *ee* (Daicel chiral ODH column (25 cm), hexanes/*i*-PrOH = 99.7/0.3, 0.3 mL/min, temp 28°C , 220 nm; tr (minor) = 23.6 min, tr (major) = 26.8 min).

(1*S*,3*S*)-1-(Dimethoxymethyl)-3-methyl-2,3-dihydro-1*H*-indene (7b)²⁷

^1H NMR (300 MHz, CDCl_3) δ : Data given above

^{13}C NMR (75 MHz, CDCl_3) δ : Data given above

5.5.16 (S)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1H-indene (16a)

The reaction was performed following the general procedure in **5.5.1**, using Ar*I (*S,S*)-**36a** (Ar*I derived from (+)-ethyl-D-lactate) (0.872 g, 2.00 mmol), *m*CPBA (77%) (0.448 g, 2.00 mmol) and (+)-CSA (0.464 g, 2.00 mmol) in TFE/DCM (1:40) (17 mL). After evaporation of the solvent, TFE/DCM (17 mL) (1:4) was added, followed by addition of alkene **1a** (0.130 g, 1.00 mmol) (dissolved in 3 mL TFE/DCM (1:4)) at -78 °C. After workup solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (3-5 % EtOAc in hexane) giving acetal **16a** (0.188 g, 0.57 mmol, 57%) as colorless oil in 56% *ee* (Sigma Aldrich chiral Astec Cellulose DMP column (25 cm), hexanes/*i*-PrOH = 99.0/1.0, 0.3 mL/min, temp 28°C, 215 nm; tr (minor) = 19.7 min, tr (major) = 21.1 min), $[\alpha]_D^{20} = -6.3$ (*c* = 0.4, CHCl₃).

(S)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1H-indene (16a)²⁷

¹H NMR (300 MHz, CDCl₃) δ : Data given above

¹³C NMR (75 MHz, CDCl₃) δ : Data given above

5.5.17 (S)-1-(bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1H-indene (16a)

The reaction was performed following the general procedure in **5.5.1**, using Ar*I (*S,S*)-**36a** (recovered from reaction mixture) (0.872 g, 2.00 mmol), *m*CPBA (77%) (0.448 g, 2.00 mmol) and (+)-CSA (0.464 g, 2.00 mmol) in TFE/DCM (1:40) (17 mL). After evaporation of the solvent, TFE/DCM (17 mL) (1:4) was added, followed by addition of alkene **1a** (0.130 g,

1.00 mmol) (dissolved in 3 mL TFE/DCM (1:4)) at -78 °C. After workup solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (3-5 % ethyl acetate in hexane) giving acetal **16a** (0.184 g, 0.560 mmol, 56%) as colorless oil in 55% *ee* (Sigma Aldrich chiral Astec Cellulose DMP column (25 cm), hexanes/*i*-PrOH = 99.0/1.0, 0.3 mL/min, temp 28°C, 215 nm; tr (minor) = 19.7 min, tr (major) = 21.1 min).

(S)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1H-indene (16a)²⁷

¹H NMR (300 MHz, CDCl₃) δ: Data given above

¹³C NMR (75 MHz, CDCl₃) δ: Data given above

5.5.18 **(S)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1H-indene (16a)**

The reaction was performed following the general procedure in **5.5.1**, using Ar*I (*S,S*)-**36a** (0.872 g, 2.00 mmol), *m*CPBA (77%) (0.448 g, 2.00 mmol) and (-)-CSA (0.464 g, 2.00 mmol) in TFE/DCM (1:40) (17 mL). After evaporation of the solvent, TFE/DCM (17 mL) (1:4) was added, followed by addition of alkene **1a** (0.130 g, 1.00 mmol) (dissolved in 3 mL TFE/DCM (1:4)) at -78 °C. After workup solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (3-5 % EtOAc in hexane) giving acetal **16a** (0.180 g, 0.550 mmol, 55%) as colorless oil in 56% *ee* (Sigma Aldrich chiral Astec Cellulose DMP column (25 cm), hexanes/*i*-PrOH = 99.0/1.0, 0.3 mL/min, temp 28°C, 215 nm; tr (minor) = 19.7 min, tr (major) = 21.1 min).

(S)-1-(Bis(2,2,2-trifluoroethoxy)methyl)-2,3-dihydro-1H-indene (16a)²⁷

¹H NMR (300 MHz, CDCl₃) δ: Data given above

¹³C NMR (75 MHz, CDCl₃) δ: Data given above

6 NMR Spectra, HPLC and GC Chromatograms

^1H NMR, 500 MHz, CDCl_3 , **1a**

^{13}C NMR, 125 MHz, CDCl_3 , **1a**

¹H NMR, 300 MHz, CDCl₃, **1b**

¹H NMR, 300 MHz, CDCl₃, **1c**

^1H NMR, 300 MHz, CDCl_3 , **1f**

^{13}C NMR, 75 MHz, CDCl_3 , **1f**

¹H NMR, 200 MHz, CDCl₃, **1g**

^{13}C NMR, 50 MHz, CDCl_3 , **1g**

^{13}C NMR, 50 MHz, CDCl_3 , **1h**

^1H NMR, 200 MHz, CDCl_3 , **1h** and **99**

¹³C NMR, 50 MHz, CDCl₃, **1hh**

¹H NMR, 200 MHz, CDCl₃, **1i**

¹H NMR, 300 MHz, CDCl₃, **1k**

^{13}C NMR, 75 MHz, CDCl_3 , **1k**

^1H NMR, 300 MHz, CDCl_3 , **11**

^{13}C NMR, 75 MHz, CDCl_3 , **11**

^1H NMR, 300 MHz, CDCl_3 , **1p**

^{13}C NMR, 75 MHz, CDCl_3 , **15aa**

¹H NMR, 300 MHz, CDCl₃, **16a**

¹³C NMR, 75 MHz, CDCl₃, **16a**

¹³C NMR, 75 MHz, CDCl₃, **16b**

¹³C NMR, 75 MHz, CDCl₃, **16j**

¹³C NMR, 75 MHz, CDCl₃, **16k**

¹H NMR, 300 MHz, CDCl₃, **16s**

^{13}C NMR, 75 MHz, CDCl_3 , **16s**

¹H NMR, 300 MHz, CDCl₃, **17b**

^{13}C NMR, 75 MHz, CDCl_3 , **17b**

^1H NMR, 300 MHz, CDCl_3 , **34**

^1H NMR, 200 MHz, DMSO- d_6 , **36b**

^{13}C NMR, 75 MHz, DMSO-d_6 , **36b**

¹H NMR, 300 MHz, CDCl₃, **36i**

^{13}C NMR, 75 MHz, CDCl_3 , **36i**

^1H NMR, 300 MHz, CDCl_3 , **36q**

¹H NMR, 300 MHz, CDCl₃, **36r**

^{13}C NMR, 75 MHz, CDCl_3 , **36r**

¹H NMR, 300 MHz, CDCl₃, **36s**

^{13}C NMR, 75 MHz, CDCl_3 , **69**

¹H NMR, 300 MHz, CDCl₃, **85f**

^1H NMR, 200 MHz, CDCl_3 , **85h**

^{13}C NMR, 50 MHz, CDCl_3 , **85h**

^{13}C NMR, 75 MHz, CDCl_3 , 85p

^1H NMR, 200 MHz, CDCl_3 , **86b**

¹H NMR, 200 MHz, CDCl₃, **87a**

^{13}C NMR, 75 MHz, CDCl_3 , **87a**

¹H NMR, 200 MHz, CDCl₃, **87b**

^{13}C NMR, 50 MHz, CDCl_3 , **87b**

¹H NMR, 300 MHz, CDCl₃, **88c**

¹H NMR, 200 MHz, CDCl₃, **98**

^{13}C NMR, 50 MHz, CDCl₃, **98**

¹H NMR, 300 MHz, CDCl₃, **117**

¹³C NMR, 75 MHz, CDCl₃, 117

¹H NMR, 300 MHz, CDCl₃, **118**

¹H NMR, 300 MHz, CDCl₃, **119**

¹³C NMR, 75 MHz, CDCl₃, 119

¹H NMR, 300 MHz, CDCl₃, **120**

^1H NMR, 200 MHz, CDCl_3 , **130**

¹H NMR, 300 MHz, CDCl₃, **138c**

¹H NMR, 300 MHz, CDCl₃, **138s**

^1H NMR, 200 MHz, CDCl_3 , **139**

^{13}C NMR, 50 MHz, CDCl_3 , **139**

¹H NMR, 200 MHz, CDCl₃, **174g**

^1H NMR, 300 MHz, CDCl_3 , 177g

¹³C NMR, 75 MHz, CDCl₃, **177g**

^1H NMR, 200 MHz, CDCl_3 , **183i**

^{13}C NMR, 50 MHz, CDCl_3 , **183i**

^{13}C NMR, 50 MHz, CDCl_3 , **184i**

¹H NMR, 200 MHz, CDCl₃, 186gg

¹H NMR, 300 MHz, CDCl₃, **190b**

¹H NMR, 200 MHz, CDCl₃, **191a**

^{13}C NMR, 50 MHz, CDCl_3 , **191a**

^{13}C NMR, 75 MHz, CDCl_3 , **192b**

¹H NMR, 300 MHz, CDCl₃, **195bb**

^1H NMR, 200 MHz, CDCl_3 , 200h

¹H NMR, 300 MHz, CDCl₃, **201h**

^{13}C NMR, 75 MHz, CDCl_3 , **201h**

¹H NMR, 200 MHz, CDCl₃, **202hh**

^1H NMR, 200 MHz, CDCl_3 , **216**

^{13}C NMR, 50 MHz, CDCl_3 , **216**

^1H NMR, 200 MHz, CDCl_3 , **218**

<Chromatogram>

1 PDA Multi 2/215nm 4nm

<Results>

PDA Ch2 215nm 4nm

Peak #	Ret. Time	Area	Area %
1	23.066	15756472	48.943
2	26.699	16436797	51.057
Total		32193269	100.000

HPLC chromatogram, (±)-7b

<Chromatogram>

1 PDA Multi 1/220nm 4nm

<Results>

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Area %
1	23.661	7431182	45.847
2	26.852	8777377	54.153
Total		16208559	100.000

HPLC chromatogram, (+)-7b

<Chromatogram>

<Results>

PDA Ch1 215nm 4nm

Peak #	Ret. Time	Area	Area %
1	16.836	11356207	50.614
2	19.251	11080899	49.386
Total		22437106	100.000

HPLC chromatogram, (±)-7f

<Chromatogram>

<Results>

PDA Ch1 215nm 4nm

Peak #	Ret. Time	Area	Area %
1	17.327	19909917	43.845
2	19.482	25500195	56.155
Total		45410112	100.000

HPLC chromatogram, (+)-7f

<Chromatogram>

<Results>

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Area %
1	15.906	2775606	49.040
2	16.767	2884269	50.960
Total		5659875	100.000

<Chromatogram>

<Results>

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Area %
1	15.763	498054	18.129
2	16.673	2249276	81.871
Total		2747330	100.000

<Chromatogram>

<Results>

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Area %
1	15.769	716438	21.429
2	16.682	2626845	78.571
Total		3343282	100.000

<Chromatogram>

1 PDA Multi 1/220nm 4nm

<Results>

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Area %
1	25.215	7923368	50.449
2	27.781	7782411	49.551
Total		15705779	100.000

<Chromatogram>

<Results>

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Area %
1	25.061	2471628	20.700
2	27.554	9468802	79.300
Total		11940430	100.000

<Chromatogram>

1 PDA Multi 1/215nm 4nm

<Results>

PDA Ch1 215nm 4nm

Peak #	Ret. Time	Area	Area %
1	42.072	9463353	49.520
2	46.262	9646800	50.480
Total		19110153	100.000

HPLC chromatogram, (±)-16a

<Chromatogram>

<Results>

PDA Ch1 215nm 4nm

Peak #	Ret. Time	Area	Area %
1	40.234	16790532	79.210
2	46.371	4406920	20.790
Total		21197452	100.000

HPLC chromatogram, (+)-16a

<Chromatogram>

1 PDA Multi 1/220nm 4nm

<Results>

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Area %
1	19.652	5053247	49.891
2	20.881	5075325	50.109
Total		10128572	100.000

HPLC chromatogram, (±)-16a

<Chromatogram>

1 PDA Multi 1/220nm 4nm

<Results>

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Area %
1	19.751	1657747	22.177
2	21.088	5817323	77.823
Total		7475069	100.000

<Chromatogram>

<Results>

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Area %
1	11.372	2985081	43.607
2	12.196	402987	5.887
3	14.863	3078024	44.965
4	16.468	379322	5.541
Total		6845413	100.000

<Chromatogram>

<Results>

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Area %
1	11.657	4348870	68.856
2	15.789	1967029	31.144
Total		6315899	100.000

HPLC chromatogram, (+)-16b

<Chromatogram>

<Results>

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Area %
1	28.500	13724298	49.585
2	31.042	13954087	50.415
Total		27678385	100.000

HPLC chromatogram, (±)16c

<Chromatogram>

1 PDA Multi 1/220nm 4nm

<Results>

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Area %
1	28.539	10222425	24.248
2	31.285	31934918	75.752
Total		42157344	100.000

<Chromatogram>

1 PDA Multi 1/220nm 4nm

<Results>

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Area %
1	10.729	17233949	46.023
2	12.849	1722936	4.601
3	14.697	16812787	44.898
4	21.418	1676773	4.478
Total		37446444	100.000

<Chromatogram>

1 PDA Multi 1/220nm 4nm

<Results>

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Area %
1	10.843	14377694	69.681
2	15.216	6255908	30.319
Total		20633601	100.000

<Chromatogram>

<Results>

PDA Ch1 215nm 4nm

Peak #	Ret. Time	Area	Area %
1	18.263	1761534	51.441
2	21.555	1662845	48.559
Total		3424379	100.000

<Chromatogram>

1 PDA Multi 1/215nm 4nm

<Results>

PDA Ch1 215nm 4nm

Peak #	Ret. Time	Area	Area %
1	18.327	2821060	81.930
2	21.658	622176	18.070
Total		3443236	100.000

<Chromatogram>

<Results>

PDA Ch1 215nm 4nm

Peak #	Ret. Time	Area	Area %
1	17.572	1022229	50.788
2	20.443	990513	49.212
Total		2012742	100.000

<Chromatogram>

<Results>

PDA Ch1 215nm 4nm

Peak #	Ret. Time	Area	Area %
1	17.417	5539235	77.778
2	20.247	1582652	22.222
Total		7121887	100.000

HPLC chromatogram, (+)-16s HPLC chromatogram, (+)-16j

<Chromatogram>

1 PDA Multi 1/215nm 4nm

<Results>

PDA Ch1 215nm 4nm

Peak #	Ret. Time	Area	Area %
1	46.428	12868113	49.560
2	50.051	13096445	50.440
Total		25964558	100.000

<Chromatogram>

<Results>

PDA Ch1 215nm 4nm

Peak #	Ret. Time	Area	Area %
1	45.265	38332955	88.708
2	49.778	4879677	11.292
Total		43212632	100.000

Data Name : C:\Documents and Settings\Laboratório\Desktop\GCsolution antigo\Data\Anees\Anees209C
Method Name : C:\GCsolution\Data\Metodos\anees chiral.gcm

Peak#	Ret.Time	Area	Height	Conc.	Unit Mark	ID#	Cmpd Name
1	26,069	5380065	328219	49,178			
2	26,583	5559999	335130	50,822	V		
Total		10940064	663349

GC chromatogram(±)-17a

Data Name : C:\Documents and Settings\Laboratório\Desktop\GCsolution antigo\Data\Anees\Anees315B.
Method Name : C:\GCsolution\Data\Metodos\anees chiral.gcm

GC chromatogram, (+)-17a

<Chromatogram>

<Results>

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Area %
1	27.372	10271406	50.936
2	34.788	9893842	49.064
Total		20165248	100.000

HPLC chromatogram, (±)-17b

<Chromatogram>

<Results>

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Area %
1	25.284	8959595	67.390
2	33.724	4335550	32.610
Total		13295145	100.000

HPLC chromatogram, (+)-17b

<Chromatogram>

1 PDA Multi 1/220nm 4nm

<Results>

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Area %
1	30.513	6634220	48.576
2	32.922	7023125	51.424
Total		13657345	100.000

HPLC chromatogram, (±)-17f

<Chromatogram>

<Results>

PDA Ch1 220nm 4nm

Peak #	Ret. Time	Area	Area %
1	30.299	22325748	66.392
2	32.892	11301514	33.608
Total		33627262	100.000

HPLC chromatogram, (+)-17f

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8 Curriculum Vitae

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Ahmad, A.; Silva, L. F., Jr. "Synthesis of Chromanes and 4*H*-Chromenes: Exploring The Oxidation of 2*H*-Chromenes and Dihydrobenzo[*b*]oxepines by Iodine(III)." *Synthesis* **2012**, 44, 3671.

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Participation in scientific Conference:

- 05/2015 Oral Presentation: 38^a Reunião Anual da Sociedade Brasileira de Química
Aguas de Lindoia, São Paulo, Brazil.
Title: Chiral Hypervalent Iodine: Asymmetric Synthesis of Indanes
- 05/2015 Poster Presentation: 38^a Reunião Anual da Sociedade Brasileira de Química
Aguas de Lindoia, São Paulo, Brazil.
Title: Chiral Hypervalent Iodine: Asymmetric Synthesis of Indanes
- 08/2014 248th ACS National Meeting & Exposition
San Francisco, CA, United States
Title: Hypervalent iodine in synthetic organic chemistry: Electrophilic alkynylation and rearrangement reactions
- 11/2013 Poster Presentation: 15th BMOS - Brazilian Meeting on Organic Synthesis
Campos do Jordão, São Paulo/SP, Brazil
Title: Asymmetric Ring Contraction Reactions Mediated by Chiral I(III)
- 09/2012 ACS on Campus
Institute of chemistry university of São Paulo, São Paulo, Brazil
- 05/2012 Poster Presentation: 35^a Reunião Anual da Sociedade Brasileira de Química
Aguas de Lindoia, São Paulo, Brazil.
Title: Ring Contraction Reactions Mediated by Hypervalent Iodine(III).
- 02/2012 Oral Presentation: Super Group Meeting on Hypervalent Iodine Chemistry Sandhamn Stockholm Sweden
Title: Exploring The Ring Contraction of Oxygen-Containing Heterocycles by Iodine(III)

- 09/2011 Poster Presentation: 14th Brazilian Meeting on Organic Synthesis
Brasília-DF, Brazil.
Title: Oxidation of Chromenes with Iodine(III).
- 08/2011 Poster Presentation: Sao Paulo Advanced School on Chemistry Natural
Products Medicinal Chemistry and Organic Synthesis Integrated
Solution for tomorrow's world.
Unicamp, Campinas, São Paulo, Brazil.
Title: Oxidation of Chromenes with Iodine(III).
- 05/2009 HEC-ICCBS–British Council Workshop on Natural Product-Based
Drugs and Other Botanical: Present Status and Future Prospects
HEJ Research Institute of Chemistry, International Center for Chemical
and Biological Sciences, University of Karachi, Karachi-75270, Sindh,
Pakistan.
- 01/2009 HEC-ICCBS–British Council Workshop on Nutraceutical Food
HEJ Research Institute of Chemistry, International Center for Chemical
and Biological Sciences, University of Karachi, Karachi-75270, Sindh,
Pakistan.
- 10/2008 Poster Presentation: 11th International Symposium on Natural product
Chemistry
HEJ Research Institute of Chemistry, International Center for Chemical
and Biological Sciences, University of Karachi, Karachi-75270, Sindh,
Pakistan.
Title: Isolation of Secondary Metabolites from Aconitum Laeve Royal

Short Courses:

- 11/2013 Fundamentals of Asymmetric Catalysis:
Speaker: Marisa C. Kozlowski, University of Pennsylvania, USA
Campos do Jordão, São Paulo/SP, Brazil
- 05/2012 Metodologias Sintéticas em Ação:
Aguas de Lindoia, São Paulo, Brazil.
- 10/2011 Ressonância Magnética Nuclear: Teoria e Aplicações na Determinação
Estrutural
Anthonio Gilberto Ferreira. UFSCAR, Brazil
Institute of chemistry university of São Paulo, São Paulo, Brazil
- 09/2011 Hypervalent Iodine Chemistry: Structure, Reactivity and Application in
Total Synthesis:
Speakers: Masahito Ochiai, University of Tokushima, Japan
Berit Olofsson, University of Stockholm, Sweden.
Luiz F. Silva, Jr, University of São Paulo, Brazil,
Brasília-DF, Brazil.

02/2008 Lecture Series on Modern Mass Spectrometry (March 08-28)
Speaker: Prof. Dr. David Smith, Department of Chemistry, University of Nebraska, Lincoln, Nebraska, USA,
HEJ Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi-75270, Pakistan. (4^{th/150} position)

Lectures Attended and Meeting with Nobel Laureate in Chemistry:

08/2011 Ei-ichi Negishi (2010), Ada Yonath (2009), Richard Royce Schrock (2005), Kurt Wüthrich (2002) and Akira Suzuki (2010)
Sao Paulo Advanced School on Chemistry Natural Products, Medicinal Chemistry and Organic Synthesis Integrated Solution for tomorrow's world.
Unicamp, Campinas, São Paulo, Brazil.

Awards and Scholarships:

06/2010 Won “Bolsa de Internacionalização” Instituto de Química, Universidade de São Paulo, São Paulo/SP, Brazil

11/2009 Scored 760 in ETS subject-GRE test USA

05/2007-07/2010 HEJ-RIC fellowship

01/2007 HEC Indigenous Scholarship awarded on the basis of GRE-NTS score 80.96 percentile

2008 Got 84.96 percentile in local general GRE test taken by National Testing Service Pakistan.

03/2006 Merit Certificate: Getting 3rd Position in order of Merit in M.Sc (Chemistry)
University of Malakand, Pakistan

Languages Skill:

English, Portuguese, Pushto, Urdu, Hindi and Arabic (basic)